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# Base-free $\beta$ -boration of $\alpha,\beta$ -unsaturated imines catalysed by $\text{Cu}_2\text{O}$ with concurrent enhancement of asymmetric induction

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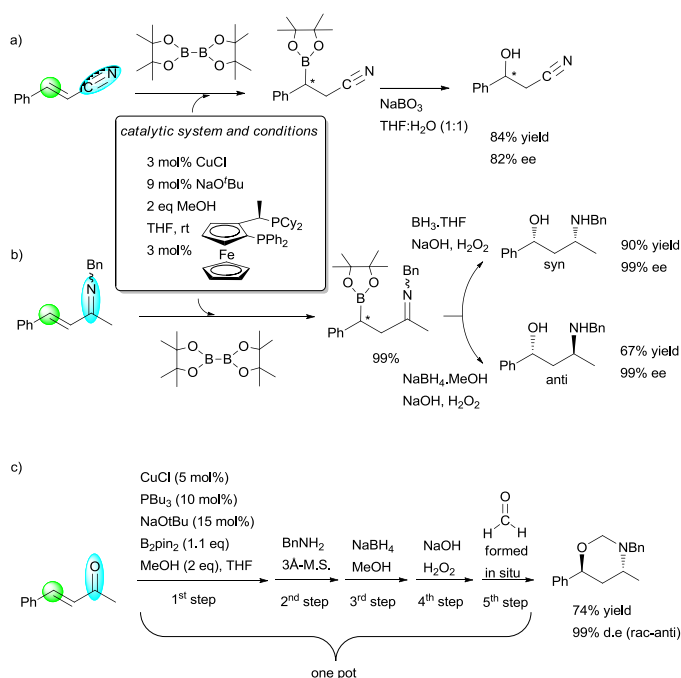
Dedication ((optional))

The stereoselective synthesis of  $\gamma$ -amino alcohols via the catalytic asymmetric  $\beta$ -boration of  $\alpha,\beta$ -unsaturated imine precursors has been streamlined with the use of  $\text{Cu}_2\text{O}$  as catalyst, readily accessible (*R*)-Binap chiral ligand and no additional base. The new simplicity of the catalytic system has the added value of *in situ* formation of the

imines, allowing access to cyclic and acyclic  $\beta$ -boryl imines. The reaction was also followed using *in situ* IR spectroscopy, demonstrating the imine formation /  $\beta$ -boration sequence and that the new catalytic system is superior to those employed for this reaction previously.

## Introduction

$\text{Cu(I)}$  catalysed asymmetric  $\beta$ -boration reactions have received considerable attention since Yun *et al.* discovered that  $\text{CuCl}$  (3 mol%) modified with bidentate Josiphos-type chiral ligands (3 mol%) could activate  $\text{B}_2\text{pin}_2$  in the presence of base (9 mol%), to deliver the Bpin moiety enantioselectively to the  $\beta$ -position of  $\alpha,\beta$ -unsaturated nitrile compounds (Scheme 1a).<sup>[1]</sup> Further efforts have been devoted to increase the scope of application of this convenient methodology to polyfunctional organoboron compounds.<sup>[2,3]</sup> We became interested in, and focussed on, the preparation of  $\gamma$ -amino alcohols in a highly enantio- and diastereo-selective manner *via* a  $\text{Cu(I)}$  mediated  $\beta$ -boration of  $\alpha,\beta$ -unsaturated imines followed by a boron-assisted *in situ* imine reduction and B-C oxidation steps (Scheme 1b).<sup>[4]</sup> We extended this strategy using *in situ* formation of the  $\alpha,\beta$ -unsaturated imines from  $\alpha,\beta$ -unsaturated aldehydes and ketones, trapping them using the  $\beta$ -boration.<sup>[5]</sup> In addition, for certain water-soluble  $\gamma$ -amino alcohol products especially, a further protection step could be performed *in situ* to give the readily isolated 1,3-oxazine derivatives in a 5 step-one pot sequence (Scheme 1c).<sup>[5]</sup>



**Scheme 1.** Strategies of precise C-B bond formation with  $\text{CuCl}$ : a) ref. 1, b) ref. 4a, c) ref. 5.

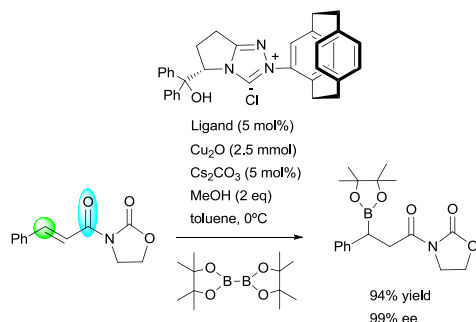
For all the  $\text{Cu}$ -mediated  $\beta$ -borations of electron deficient olefins reported to date, the addition of base has always been required,<sup>[6]</sup> unless preformed  $(\text{NHC})\text{CuOR}$  species ( $\text{NHC}$  = N-heterocyclic carbene ligands) and  $\text{Cu}(\text{OH})_2/\text{L}$  are used to activate the  $\text{B}_2\text{pin}_2$ <sup>[7,8]</sup> or  $\text{sp}^2\text{-sp}^3$  hybridised mixed diboron reagents transmetallate with  $\text{CuCl}$  to provide the  $\text{CuBpin}$  reactive species.<sup>[9]</sup> We became interested in exploring the use of  $\text{Cu}_2\text{O}$  as precursor of the active catalytic system for the  $\beta$ -boration of  $\alpha,\beta$ -unsaturated imines. Most importantly, this could potentially

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behave as a novel base-free system, as well as potentially being asymmetric when used in the presence of suitable compatible chiral ligands. This hypothesis is based on the possibility that Cu<sub>2</sub>O could interact with MeOH to generate a Cu(I)-alkoxide or -hydroxide species. To the best of our knowledge, there is only one example of asymmetric induction upon C-B bond formation mediated by Cu<sub>2</sub>O in the  $\beta$ -boration of  $\alpha,\beta$ -unsaturated *N*-acyloxazolidinones using a chiral bicyclic 1,2,4-triazolium salt (Scheme 2) and Cs<sub>2</sub>CO<sub>3</sub> base.<sup>[10]</sup> Our objective was to investigate, and highlight, the benefits of Cu<sub>2</sub>O as a cheap catalyst precursor, avoiding the addition of an external base, and modify the Cu<sub>2</sub>O with commercially available chiral ligands, such as (*R*)-BINAP, to promote an efficient enantioselective catalytic system.

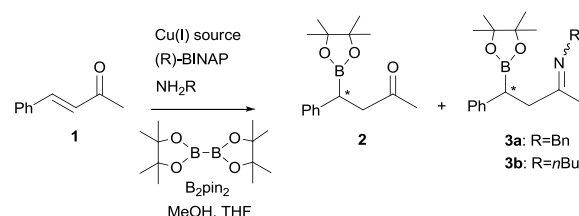


**Scheme 2.** Cu<sub>2</sub>O mediated  $\beta$ -boration of *N*-cinnamoyloxazolidin-2-one with chiral triazolium salt.

## Results and Discussion

Our study began with the  $\beta$ -boration of 4-phenyl-3-buten-2-one (**1**) as a model substrate, and bis(pinacolato)diboron (B<sub>2</sub>pin<sub>2</sub>) as the diboron reagent. Two Cu(I) sources were selected; CuCl (3 mol%) and Cu<sub>2</sub>O (1.5 mol%), in order to compare their relative activities as catalyst precursors, in the presence of (*R*)-BINAP. In an initial set of experiments, the substrate **1** was not converted into the  $\beta$ -borated ketone **2** in the absence of BnNH<sub>2</sub> (Table 1, entries 1 and 6), however, with the increasing addition of BnNH<sub>2</sub> (10 – 100 mol%) progressive formation of the  $\beta$ -borated imine **3a** occurred with different efficiency, depending on the copper source. When the CuCl-(*R*)-BINAP catalytic system was used, the  $\beta$ -borated ketone **2** was still the main product at low amine loadings (Table 1, entries 2-3). When the percentage of amine increased from 50 to 100% in the CuCl mediated reaction, only  $\beta$ -borated imine **3a** was observed, although substrate **1** still remained even in the presence of 100% of BnNH<sub>2</sub> (Table 1, entries 4-5). Remarkably however, when the Cu<sub>2</sub>O-(*R*)-BINAP catalyst system was used for the  $\beta$ -boration of **1**, the percentage of the  $\beta$ -borated imine **3a** formed was, in all cases, close to the percentage of amine present (Table 1, entries 7-10). This shows that Cu<sub>2</sub>O favours trapping of the “*in situ*” formed  $\alpha,\beta$ -unsaturated imine by catalysing its transformation into the corresponding  $\beta$ -borated imine **3a**. In addition, the beneficial influence of Cu<sub>2</sub>O could also be extended to the asymmetric induction of the C-B bond formation step. While the CuCl-(*R*)-BINAP catalytic system provided the  $\beta$ -borated imine with e.e. values around 85-89%, the Cu<sub>2</sub>O-(*R*)-BINAP system promoted the enantioselective formation on **3a** in up to 99 % of e.e. (Table 1). It is noteworthy also that the remaining  $\beta$ -borated ketone **2** was obtained always with e.e. values between 16-22%, and that an excess of (*R*)-BINAP in the reaction media did not change the reaction outcome (Table 1, entry 11). The same was also found to be the case with higher loadings of Cu<sub>2</sub>O, (Table 1, entry 12). Interestingly, when a Cu(II) source was used instead, i.e. CuO, the catalytic system CuO-(*R*)-

BINAP did convert the  $\alpha,\beta$ -unsaturated ketone **1** into the  $\beta$ -borated imine **3a**, however, with only 71% of conversion and only moderate e.e.s (Table 1, entry 13). Apart from the two previous reports of Cu(II) catalysed  $\beta$ -boration of  $\alpha,\beta$ -unsaturated carbonyl compounds,<sup>[8,11]</sup> to the best of our knowledge, this is the first example of Cu(II) catalysing the  $\beta$ -boration of  $\alpha,\beta$ -unsaturated imines. It is also interesting to observe that the nature of the amine used in the reaction seems to be crucial for the enantioselection. Hence, when the  $\beta$ -boration of **1** with Cu<sub>2</sub>O-(*R*)-BINAP was carried out in the presence of 100 mol% of NH<sub>2</sub>Bu, the  $\beta$ -borated imine **3b** was quantitatively formed, but only with 27% e.e. (Table 1, entry 14).

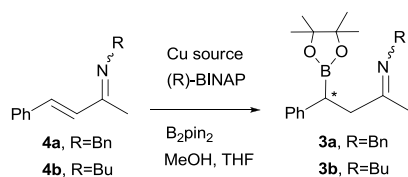


**Table 1.** Cu-(*R*)-BINAP mediates  $\beta$ -boration of activated olefins.<sup>[a]</sup>

Entry	Cu(I)	RNH <sub>2</sub> (mol%)	Conv (%) <sup>[b]</sup>	<b>2</b> (%) <sup>[b]</sup>	e.e (%) <sup>[c]</sup>	<b>3</b> (%) <sup>[b]</sup> [Y (%) <sup>[d]</sup> ]	e.e (%) <sup>[c]</sup>
1	CuCl	---	0	---	---	---	---
2	CuCl	BnNH <sub>2</sub> (10)	24	21	21 (S)	3	nd
3	CuCl	BnNH <sub>2</sub> (25)	35	32	22 (S)	3	nd
4	CuCl	BnNH <sub>2</sub> (50)	36	---	---	36	89 (S)
5	CuCl	BnNH <sub>2</sub> (100)	71	---	---	71	85 (S)
6	Cu <sub>2</sub> O	---	0	---	---	---	---
7	Cu <sub>2</sub> O	BnNH <sub>2</sub> (10)	43	37	16 (S)	6	99 (S)
8	Cu <sub>2</sub> O	BnNH <sub>2</sub> (25)	53	32	22 (S)	21	99 (S)
9	Cu <sub>2</sub> O	BnNH <sub>2</sub> (50)	57	11	nd	46	95 (S)
10	Cu <sub>2</sub> O	BnNH <sub>2</sub> (100)	>99	0	nd	99	95 (S)
11 <sup>[d]</sup>	Cu <sub>2</sub> O	BnNH <sub>2</sub> (100)	>99	0	nd	99	93 (S)
12 <sup>[e]</sup>	Cu <sub>2</sub> O	BnNH <sub>2</sub> (100)	>99	0	nd	>99 [89]	95 (S)
13 <sup>[f]</sup>	CuO	BnNH <sub>2</sub> (100)	71	0	nd	71	73 (S)
14	Cu <sub>2</sub> O	n-BuNH <sub>2</sub> (100)	>99	---	---	99	27 <sup>[g]</sup> (S)

<sup>[a]</sup> Reaction conditions: substrate (0.25 mmol), CuCl (3 mol%) or Cu<sub>2</sub>O (1.5 mol%), (*R*)-BINAP (3 mol%), B<sub>2</sub>pin<sub>2</sub> (1.1 equiv.), MeOH (2.5 equiv.), THF (1 mL) 25 °C, 16 h. <sup>[b]</sup> Conversion and selectivity calculated from consumed substrate by <sup>1</sup>H NMR. <sup>[c]</sup> E.e. calculated by HPLC-UV as an average of two results. <sup>[d]</sup> Cu<sub>2</sub>O (1.5 mol%), (*R*)-BINAP (6 mol%). <sup>[e]</sup> Cu<sub>2</sub>O (3 mol%), (*R*)-BINAP (6 mol%). <sup>[f]</sup> CuO (3 mol%), (*R*)-BINAP (6 mol%). <sup>[g]</sup> E.e. calculated on the hydrolysed ketone via HPLC-MS.

To confirm the benefits of Cu<sub>2</sub>O-(*R*)-BINAP on the enantioselective formation of the β-borated imines **3**, we became interested in isolating the α,β-unsaturated imines, such as (*E*)-1-phenyl-*N*-(4-phenylbut-3-en-2-ylidene)methanamine (**4a**), and performing the β-boration on that substrate to compare with the reactions carried out from the *in situ* reaction of α,β-unsaturated ketone **1** + BnNH<sub>2</sub>. In the absence of base, Cu<sub>2</sub>O-(*R*)-BINAP catalysed the formation of **3a** with high enantioselectivity, while CuCl-(*R*)-BINAP was inactive (Table 2, entries 1 and 2). The addition of 10 mol% NaOtBu or Cs<sub>2</sub>CO<sub>3</sub> to the CuCl-(*R*)-BINAP catalytic system favoured the formation of **3a**, but resulting in a racemic product (Table 2, entries 4 and 5). However, the addition of 10 mol% BnNH<sub>2</sub> as base did not favour the β-boration of the imine. The role of the base is expected to favour transmetalation between CuCl and B<sub>2</sub>pin<sub>2</sub>,<sup>[6]</sup> however, it seems that only inorganic bases assist this step. In contrast, when Cu<sub>2</sub>O was used, no additional base was required to promote the transmetalation and in addition, the enantioselectivity was significantly higher.



**Table 2.** Cu-(*R*)-BINAP mediates β-boration of activated olefins<sup>[a]</sup>

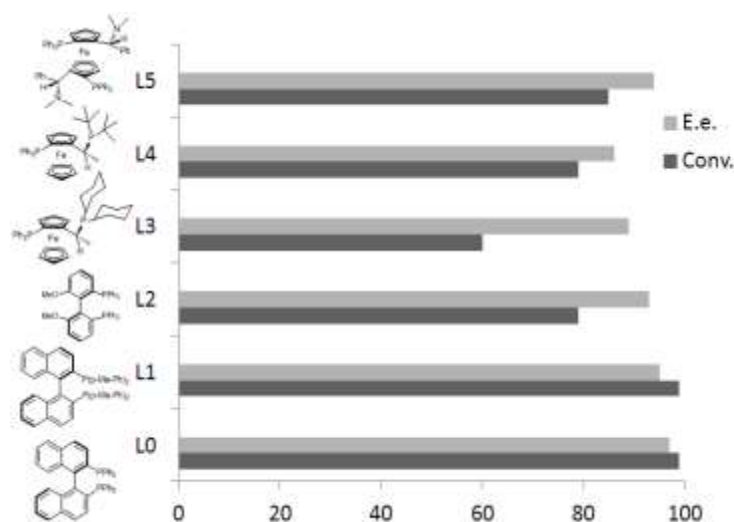
Entry	Imine	Cu(I)	Base (mol%)	Conv (%) <sup>[b]</sup>	<b>3</b> (%) <sup>[b]</sup> [ <i>Y</i> (%)]	e.e (%) <sup>[c]</sup>
1	<b>4a</b>	Cu <sub>2</sub> O	---	>99	>99	87 (S)
2	"	CuCl	---	0	---	--
3	"	CuCl	BnNH <sub>2</sub> (10)	0	---	--
4	"	CuCl	Cs <sub>2</sub> CO <sub>3</sub> (10)	>99	>99	0
5	"	CuCl	NaOtBu (10)	>99	>99	0
6	"	(CH <sub>3</sub> CN) <sub>4</sub> CuPF <sub>6</sub>	---	>99	>99	85 (S)
7	"	CuO	---	15	15	69 (S)
8	<b>4b</b>	Cu <sub>2</sub> O	---	99	99	7 <sup>[d]</sup> (S)
9	"	(CH <sub>3</sub> CN) <sub>4</sub> CuPF <sub>6</sub>	---	99	99	8 <sup>[d]</sup> (S)
10	"	CuCl	---	<5	---	--

<sup>[a]</sup> Reaction conditions: α,β-unsaturated imine (0.25 mmol), CuCl (3 mol%)/(*R*)-BINAP (6 mol%), (CH<sub>3</sub>CN)<sub>4</sub>CuPF<sub>6</sub> (3 mol%)/(*R*)-BINAP (6 mol%) or Cu<sub>2</sub>O (1.5 mol%)/(*R*)-BINAP (3 mol%), B<sub>2</sub>pin<sub>2</sub> (1.1 equiv.), MeOH (2.5 equiv.), THF (1 mL) 25 °C, 16 h. <sup>[b]</sup> Conversion calculated from consumed substrate by <sup>1</sup>H NMR. <sup>[c]</sup> E.e. calculated by HPLC-UV as an average of two results. <sup>[d]</sup> E.e. calculated from the hydrolysed ketone via HPLC-MS.

The lack of a coordinating anion on the Cu(I) catalytic system appears to be the key factor in avoiding the need for additional base in the β-boration. This is clearly demonstrated by using Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> modified with (*R*)-BINAP to catalyse the asymmetric β-boration of **4a** (Table 2, entry 6), which is similar to using Cu<sub>2</sub>O, though Cu<sub>2</sub>O is significantly cheaper. Interestingly, when Cu(II) was also explored for catalysing the reaction, we observed that the CuO-(*R*)-BINAP catalytic system was almost inactive towards the β-boration of **4a** (Table 2, entry 7). If we compare the latter result with the CuO-(*R*)-BINAP catalysed β-boration of **1** in the presence of 1 eq. of BnNH<sub>2</sub> (Table 1, entry 13), we can conclude that the Cu(II) catalytic system studied needs a

base to activate the diboron source. From these observations, it is clear that the use of Cu<sub>2</sub>O is especially beneficial because it can be used in the absence of bases to promote the desired β-boration reaction. As far as the influence of the N-substituent is concerned, when Cu<sub>2</sub>O-(*R*)-BINAP mediated the β-boration of (*E*)-*N*-(4-phenylbut-3-en-2-ylidene)butan-1-amine (**4b**), also without base the β-borated imine **3b** was quantitatively formed but with low enantioselectivity (Table 2, entry 8). Similar behaviour was observed when Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> was the copper source, although CuCl resulted inactive (Table 2, entries 9 and 10). The observation of low enantioselectivity in entries 8 and 9 (Table 2) also confirms the important role of the N-substituent in achieving high asymmetric induction.

The synergy between Cu<sub>2</sub>O and (*R*)-BINAP (**L0**) was further demonstrated when we explored the influence of alternative bidentate chiral ligands such as (*R*)-Tol-BINAP (**L1**), (*R*)-Ph-MeOBiphep (**L2**), Josiphos (**L3**, **L4**) and Mandiphos (**L5**) type ligands. Remarkably, the cheapest ligand, (*R*)-BINAP, provided the best influence on the enantioselective Cu<sub>2</sub>O-catalysed β-boration of 4-phenyl-3-buten-2-one **1**, in the presence of 1 eq. of BnNH<sub>2</sub> and B<sub>2</sub>pin<sub>2</sub> (Figure 1).

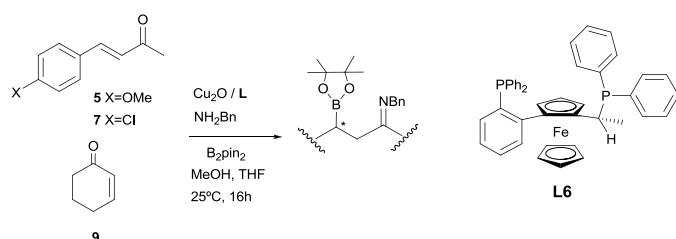


**Figure 1.** Cu<sub>2</sub>O (1.5 mol%)/L (3 mol%), catalysed the β-boration of 4-phenyl-3-buten-2-one (**1**) (0.25 mmol), in the presence of BnNH<sub>2</sub> (1eq.) and B<sub>2</sub>pin<sub>2</sub> (1.1 eq.), MeOH (2.5 equiv.), THF (1 mL) 25 °C, 16 h.

The substrate scope of the β-boration of α,β-unsaturated imines, formed *in situ* from the corresponding α,β-unsaturated ketones and BnNH<sub>2</sub>, was surveyed using the Cu<sub>2</sub>O-(*R*)-BINAP catalytic system and compared also with the influence of alternative chiral ligands. For the transformation of 4-(*p*-MeO-phenyl)-3-buten-2-one (**5**) into the β-borated imine **6** (Table 3, entry 1), the Cu<sub>2</sub>O-(*R*)-BINAP and Cu<sub>2</sub>O-(*R*)-Tol-BINAP catalytic systems provided moderate conversions but high e.e.s. On the contrary, the Cu<sub>2</sub>O system modified with the MeOBiphep (**L2**) and Mandiphos (**L5**) ligands favoured high conversions, but provided only moderate enantioselectivity. When the substrate studied was the more electron deficient olefin 4-(*p*-Cl-phenyl)-3-buten-2-one (**7**) (Table 3, entry 2), all the catalytic systems explored provided a quantitative β-borated product **8** with only moderate enantioselectivity.

Having examined acyclic substrates, the β-boration of cyclic α,β-unsaturated imine substrates was also studied. Towards this end, we found that cyclohexenone (**9**) could be efficiently converted

into the desired product **10** with Cu<sub>2</sub>O-modified by (*R*)-BINAP (**L0**), (*R*)-Tol-BINAP (**L1**) and MeOBiphep (**L2**), however, the enantioselectivity was only moderate (Table 3, entry 3). In contrast, when the influence of a Walphos-type ligand **L6** was explored, we observed that although conversion to the product **10** was low (20%), the e.e. was the highest for this substrate (92%) (Table 3, entry 3). It is important to note that although this is the first approach to the enantioselective formation of cyclic  $\beta$ -boryl imine derivatives, the *base-free* asymmetric induction provided by Cu<sub>2</sub>O modified with ligands **L0**, **L1** and **L6** is in complete agreement with the previous work of Yun and co-workers,<sup>[2f]</sup> who reported that CuCl+base mediated the enantioselective  $\beta$ -boration of cyclohexenone (Table 3, entry 4). Since the corresponding  $\alpha,\beta$ -unsaturated cyclic imine, 1-phenyl-*N*-(cyclohexenyl)methanamine, could not be isolated to be  $\beta$ -bored, the alternative *in situ* formation of the imine, followed by  $\beta$ -boration trapping by means of the Cu<sub>2</sub>O-based system, represents a simple method to obtain an enantiomerically enriched  $\beta$ -bored imine **10**.



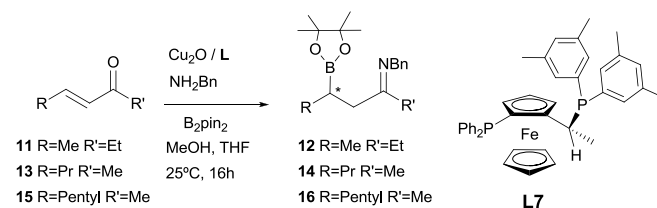
**Table 3** Substrate scope for the Cu<sub>2</sub>O mediated asymmetric  $\beta$ -boration of *in situ*-formed  $\alpha,\beta$ -unsaturated imines.<sup>[a]</sup>

Entry	Product	Ligand	Conv (%) <sup>[b]</sup> [IY (%)]	e.e. (%) <sup>[c]</sup>
1		( <i>R</i> )-BINAP ( <b>L0</b> )	67 [45]	86 (S)
		<b>L1</b>	71	82 (S)
		<b>L2</b>	85 [60]	49 ( <i>R</i> )
		<b>L5</b>	99	35 ( <i>R</i> )
2		( <i>R</i> )-BINAP ( <b>L0</b> )	99 [87]	48 (S)
		<b>L1</b>	99	47 (S)
		<b>L2</b>	99 [85]	58 (S)
		<b>L5</b>	99	35 (S)
3		( <i>R</i> )-BINAP ( <b>L0</b> )	99 [89]	39 (S) <sup>[d]</sup>
		<b>L1</b>	99	65 (S) <sup>[d]</sup>
		<b>L2</b>	97	30 (S) <sup>[d]</sup>
		<b>L6</b>	20	92 ( <i>R</i> ) <sup>[d]</sup>
4		( <i>R</i> )-BINAP ( <b>L0</b> )	93 (2 h)	40 (R) <sup>[e]</sup>
		<b>L1</b>	93 (2 h)	63 (S) <sup>[e]</sup>
		<b>L6</b>	90 (24 h)	90 (S) <sup>[e]</sup>

<sup>[a]</sup> Reaction conditions:  $\alpha,\beta$ -unsaturated imine (0.25 mmol), Cu<sub>2</sub>O (3 mol%), L (6 mol%), B<sub>2</sub>pin<sub>2</sub> (1.1 equiv.), MeOH (2.5 equiv.), THF (1.3 mL) 25 °C, 16 h. <sup>[b]</sup> Conversion calculated from consumed substrate by <sup>1</sup>H NMR spectroscopy. <sup>[c]</sup> E.e. calculated by HPLC-UV as an average of two results. <sup>[d]</sup> e.e. Calculated on the hydrolysed  $\beta$ -bored ketone via HPLC-MS. <sup>[e]</sup> Ref. 2f, CuCl (3 mol%), NaOtBu (3 mol%), L (3 mol%).

Another set of substrates we were keen to explore as suitable candidates for the *in situ* imine formation, followed by  $\beta$ -boration in the presence of Cu<sub>2</sub>O/L, were the aliphatic, open-chain,  $\alpha,\beta$ -unsaturated ketones, 4-hexen-3-one (**11**), 3-hepten-2-one (**13**) and 3-nonen-2-one (**15**). The corresponding  $\alpha,\beta$ -unsaturated imines could also not be isolated in order to perform a copper-catalysed  $\beta$ -boration, and hence, the *in situ* protocol gave us an

alternative approach towards the aliphatic  $\beta$ -bored imines (see Table 4). In all cases, a secondary product ( $\beta$ -amino ketone) could be identified due to the competitive aza-Michael addition reaction of the amine to the  $\alpha,\beta$ -unsaturated ketones.<sup>[12]</sup> Therefore, the selectivity of the desired  $\beta$ -bored imine varied from moderate to high, depending on the substrate and the nature of the chiral ligand. When the substrate was 3-hepten-2-one **13**, the two-step reaction occurred efficiently to give a high conversion to the  $\beta$ -bored imine (up to 93%, Table 4, entry 2). The bidentate chiral ligand that induced the highest enantioselectivity in the Cu<sub>2</sub>O mediated imine formation /  $\beta$ -boration of ketones **13** and **15** was the Josiphos-type ligand **L7** (e.e.s up to 92%, Table 4).



**Table 4** Substrate scope for the Cu<sub>2</sub>O mediated asymmetric  $\beta$ -boration of *in situ*-formed  $\alpha,\beta$ -unsaturated imines from aliphatic open chain  $\alpha,\beta$ -unsaturated ketones.<sup>[a]</sup>

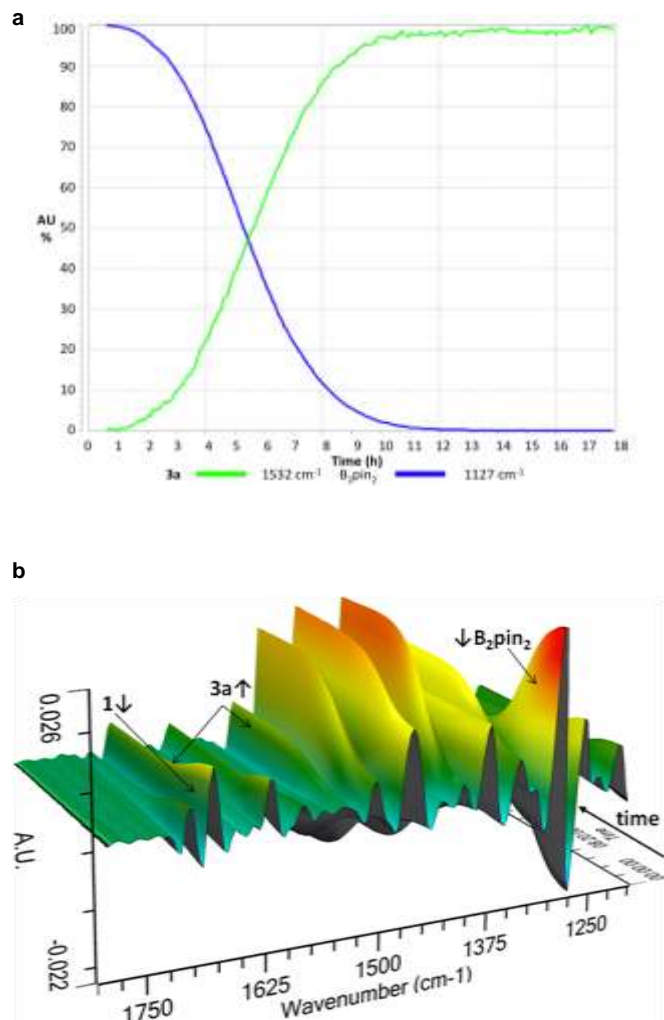
Entry	Product	Ligand	Conv (%) <sup>[b]</sup>	Sel(%) <sup>[c]</sup> [IY (%)]	e.e. (%) <sup>[d]</sup>
1		( <i>R</i> )-BINAP	99	55 [35]	66 (+)
		<b>L1</b>	99	63	61(+)
		<b>L2</b>	99	68 [32]	50 (+)
		<b>L7</b>	99	54	80 (+)
2		( <i>R</i> )-BINAP	99	70 [63]	62 (+)
		<b>L1</b>	99	93	60 (+)
		<b>L2</b>	99	90 [76]	64 (+)
		<b>L7</b>	99	52	73 (+)
3		( <i>R</i> )-BINAP	99	71 [56]	70 (+)
		<b>L1</b>	99	77	66 (+)
		<b>L2</b>	99	58 [43]	64 (+)
		<b>L7</b>	99	64	92 (+)

<sup>[a]</sup> Reaction conditions:  $\alpha,\beta$ -unsaturated imine (0.25 mmol), Cu<sub>2</sub>O (3 mol%), L (6 mol%), B<sub>2</sub>pin<sub>2</sub> (1.1 equiv.), MeOH (2.5 equiv.), THF (1.3 mL) 25 °C, 16 h. <sup>[b]</sup> Conversion calculated from consumed substrate by <sup>1</sup>H NMR spectroscopy. <sup>[c]</sup> Selectivity calculated by <sup>1</sup>H NMR spectroscopy, with the  $\beta$ -amino ketone as by-product. <sup>[d]</sup> e.e. Calculated via HPLC-MS.

We further examined the *base-free* Cu<sub>2</sub>O-**L1**-B<sub>2</sub>pin<sub>2</sub> catalytic system and the analogous CuCl-**L1**-B<sub>2</sub>pin<sub>2</sub> system, by following the *in situ* imine formation /  $\beta$ -boration reaction between **1** (1 eq.) and BnNH<sub>2</sub> (1 eq.) using *in situ* IR spectroscopy (ReactIR, Figs. 2 and 3 respectively). We were intrigued by the different roles of Cu<sub>2</sub>O versus CuCl in the intrinsic  $\alpha,\beta$ -unsaturated imine formation and subsequent  $\beta$ -boration to produce the  $\beta$ -boryl imine **3a**. In each case, the initial 20 min period was cropped to allow for addition and mixing of reagents, imine formation, and then addition of MeOH which initiates the  $\beta$ -boration (as measured by the rate-of-decrease of the B<sub>2</sub>pin<sub>2</sub>, blue line in both Figs. 2 and 3).

Using the Cu<sub>2</sub>O system for the *in situ* formed  $\alpha,\beta$ -unsaturated imine **4a**, the reaction follows a first-order-like reaction profile (Fig. 2a), reaching completion after ca. 10 h (Note: subsequent addition of borohydride-MeOH can be followed readily by ReactIR, with the imine reduction clearly visible, see ESI). The

Cu<sub>2</sub>O system does not seem to catalyse the imine formation. Interestingly, the formation of **3a** almost mirrors the rate-of-decrease of the B<sub>2</sub>pin<sub>2</sub> (see Fig. 2b: the direct graphical output of Fig. 2a) and is faster than the rate of decrease of enone **1** under direct borlylation conditions, thus providing further evidence that the reaction proceeds through imine formation /  $\beta$ -boration sequence, and not  $\beta$ -boration of **1** followed by subsequent imine formation.

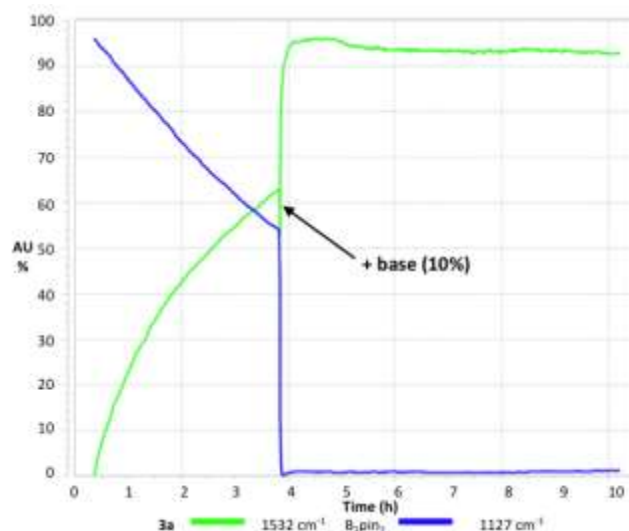


**Figure 2. a)** ReactIR derived reaction profile showing synchronous *in situ* imine **4a** formation from ketone **1** and Cu<sub>2</sub>O-L1 catalysed borylation, forming  $\beta$ -boryl imine **3a**. Due to overlapping C=O (substrate) and C=N (product) stretches, an alternative stretch at 1532 cm<sup>-1</sup> was followed to monitor the formation of **3a**; **b)** The corresponding ReactIR graphical output (with 2<sup>nd</sup> derivative base-line correction) showing synchronous *in situ* imine **4a** formation from ketone **1** and Cu<sub>2</sub>O-L1 catalysed borylation, forming  $\beta$ -boryl imine **3a**.

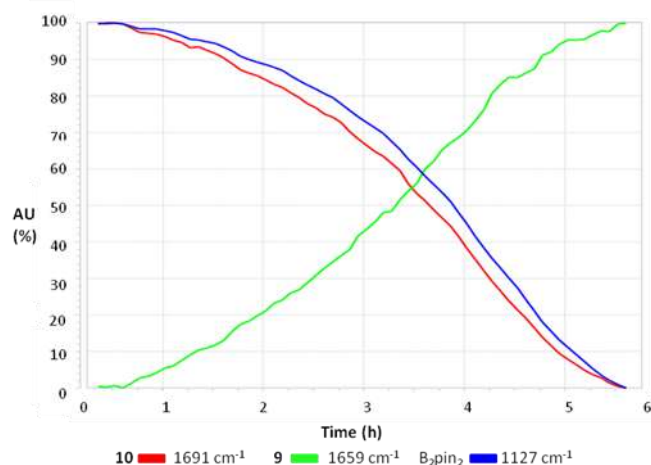
These results highlight that  $\alpha,\beta$ -unsaturated imines are considerably more reactive than the corresponding  $\alpha,\beta$ -unsaturated ketones, in the Cu-catalysed  $\beta$ -boration reaction. In stark contrast, when the identical reaction is carried out using CuCl (Fig. 3) in place of Cu<sub>2</sub>O, the reaction shows completely different kinetic behaviour and does not proceed to completion (even after 24 h, see ESI). However, when base was added (NaOtBu, 10 mol%) at 4 h, the key role of the base was

demonstrated, resulting in the rapid and complete loss of the B<sub>2</sub>pin<sub>2</sub> and full conversion of **4a** to the  $\beta$ -borylated imine **3a**.

Next, we explored the efficiency of the *base-free* Cu<sub>2</sub>O-L1-B<sub>2</sub>pin<sub>2</sub> catalytic system in the *in situ* imine formation-borylation of the aliphatic cyclic  $\alpha,\beta$ -unsaturated ketone **9**. We became interested to determine the rate of formation of  $\beta$ -borylated imine **10** and compare it with the previously observed for the formation of  $\beta$ -borylated imine **3a**. With the *in situ* IR spectroscopy (ReactIR) data shown in Fig. 4), similar behaviour of the *in situ* cyclohexenone-derived imine  $\beta$ -boration to that of the chalcone-ketone derivative substrate was observed, i.e. the decrease of substrate **9** and B<sub>2</sub>pin<sub>2</sub> was synchronous to the increase in  $\beta$ -boryl imine **10**. However, the reaction was slightly faster, being complete in essentially 6 h (for **10**) vs. 10 h (for **3a**). This strongly suggests that: 1) *N*-Cu chelation is not necessary for the  $\alpha,\beta$ -unsaturated imine  $\beta$ -boration reaction; 2) an *s-cis* conformation of the activated imine more reactive towards  $\beta$ -boration is not required. Indeed, the fixed *s-trans* conformation derived from the cyclohexenone imine is more reactive, clearly illustrating this point.



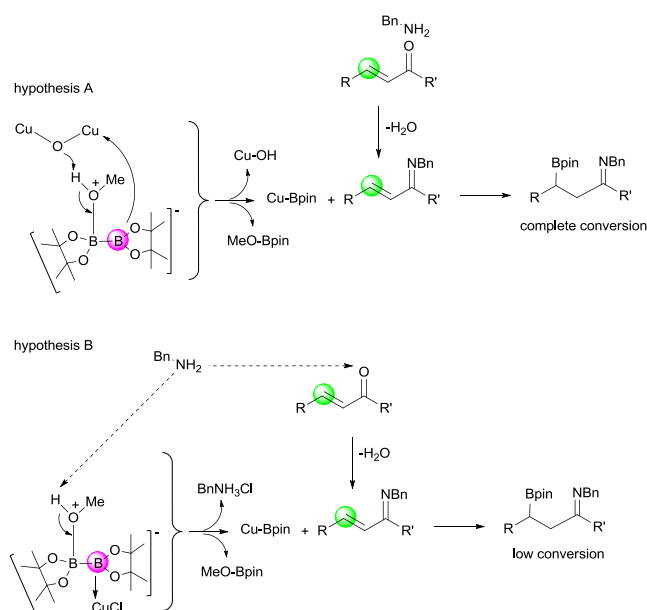
**Figure 3.** ReactIR derived reaction profile showing synchronous *in situ* imine **4a** formation and borylation to give the resulting imine **3a** [CuCl-L1+ the addition of NaOtBu (10 mol%) after 4 h]. The peak-fluctuation at 4 h is a result of the mixing upon addition of base.



**Figure 4.** ReactIR derived reaction profile showing synchronous *in situ* imine derivative of ketone **9** and Cu<sub>2</sub>O-L1 catalysed borylation, forming  $\beta$ -boryl imine **10**.



Scheme 3 illustrates, in hypothesis A, a plausible interaction between Cu<sub>2</sub>O, MeOH and B<sub>2</sub>pin<sub>2</sub>, to provide the corresponding CuBpin nucleophilic species and an additional Cu(OH) species ready to transmetallate further with B<sub>2</sub>pin<sub>2</sub>. In this hypothetical view, the BnNH<sub>2</sub> seems to be exclusively involved in imine formation. However, when CuCl is used as the copper source, the BnNH<sub>2</sub> may have a partial role in inefficiently activating MeOH and forming the imine (Scheme 3, hypothesis B). This would explain why the reactions carried out without base addition and using CuCl do not proceed to completion effectively and low or zero activity that is observed in the β-boration of the isolated imine. Of course, as shown in Fig. 3, the addition of base is able to recover the catalytic activity, but even this does not match the newly developed efficient Cu<sub>2</sub>O system, as demonstrated by Fig. 2. In addition, the enantioselectivity could be increased by the absence of external base which favors background reactions.



**Scheme 3.** Hypothetical activation of B<sub>2</sub>pin<sub>2</sub> with Cu<sub>2</sub>O and CuCl.

## Conclusion

In conclusion, we have found that Cu<sub>2</sub>O guarantees the clean and efficient β-boration of unsaturated imines in the absence of bases. Both the *in situ* formation of the α,β-unsaturated imine and concurrent β-boration of this intermediate can be readily followed by *in situ* IR spectroscopy, which shows a clean and rapid *pseudo* first order reaction, which is slightly faster for a cyclic enone-derived imine compared with the acyclic system. The activation of the diboron reagent, B<sub>2</sub>pin<sub>2</sub>, with Cu<sub>2</sub>O does not need external base to form the CuBpin moiety, and indeed, this system behaves similarly to the CuCl system once base is added, though the Cu<sub>2</sub>O system is more efficient, particularly as revealed by *in situ* IR. The modification of Cu<sub>2</sub>O with commercially available chiral ligands, such as (*R*)-BINAP, enhances the asymmetric induction on the C-B bond formation, principally when the Bn group is attached to the imine.

## Experimental Section

### Experimental procedure for the copper/(*R*)-BINAP catalysed β-boration of *in situ* formed α,β-unsaturated imines with bis(pinacolato)diboron.

Cu(I) salts (1.5–3 mol%), (*R*)-BINAP (3–6 mol%, 0.0075–0.015 mmol, 4.7–9.3 mg) were transferred to a Schlenk tube and dissolved in THF (1 mL) under Ar. After 15 min, bis(pinacolato)diboron (70 mg, 0.28 mmol, 1.1 equiv.) was added to the solution and stirred during 10 min. Then, benzylamine (0.25 mmol, 27 μL) and α,β-unsaturated ketone (0.25 mmol) were added at the same time. Finally, MeOH (0.55 mmol, 25 μL, 2.5 equiv.) was added and the reaction mixture was left to stir overnight at RT. The reaction products and conversions were determined by <sup>1</sup>H NMR. The e.e.s were determined directly by HPLC-UV or HPLC-MS for the hydrolysed β-borated ketone.

### Screening of chiral ligands for the asymmetric Cu<sub>2</sub>O/L catalysed β-boration of α,β-unsaturated imines formed *in situ*.

Cu<sub>2</sub>O (3 mol%, 0.0075 mmol, 1 mg), chiral diphosphine (6 mol%, 0.015 mmol) and THF (1 mL) were transferred into a Radley's Carousel 12 place reactor under Ar. The mixture was stirred for 15 min at room temperature. Bis(pinacolato)diboron (0.28 mmol, 70 mg, 1.1 equiv.) was added and the solution was stirred for 10 min. Then benzylamine (0.25 mmol, 27 μL, 1 equiv.) and the α,β-unsaturated ketone (0.25 mmol) were added simultaneously, followed by the addition of MeOH (0.55 mmol, 25 μL, 2.5 equiv.). The reaction mixture was stirred overnight at RT. The products obtained were analyzed by <sup>1</sup>H NMR spectroscopy to determine the conversion towards the desired β-boryl imine products. The enantiomeric excess of **3a**, **6** and **8**, were determined directly by HPLC-UV, otherwise, the enantiomeric excess of the other β-boryl imines **3b**, **10**, **12**, **14**, **16** was determined by HPLC-MS from the corresponding β-boryl ketone derivative obtained by hydrolysis.

**ReactIR** All *in situ* IR spectroscopy experiments (ReactIR) were carried out on the following instrument: ReactIR 15 with MCT detector; HappGenzel, DiComp (Diamond) probe connected via AgX 9.5 mm – 2 m fiber (Silver Halide); Sampling 2500 to 650 cm<sup>-1</sup>, 8 wave number resolution. Reaction performed on a 1 mmol scale using the standard protocol.

## Acknowledgements

We thank the EPSRC for a grant to A. D. J. C., MEC for funding (CTQ2010-16226) and C. S. for FPU grant. We thank AllyChem and Solvias for the donation of diboron reagents and chiral auxiliaries.

**Keywords:** α,β-unsaturated imines • β-boration • Cu<sub>2</sub>O • ReactIR • β-boryl imines

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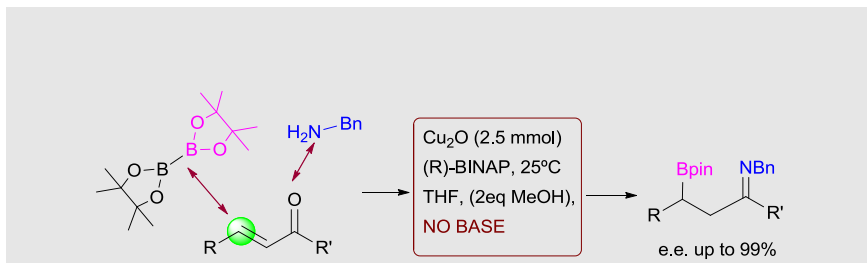
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## Entry for the Table of Contents (Please choose one layout only)

Layout 2:

### FULL PAPER



Adam D. J. Calow,<sup>[b]</sup> Cristina Solé,<sup>[a]</sup>  
Andrew Whiting,<sup>\*,[b]</sup> Elena Fernández<sup>\*,[a]</sup>

Page No. – Page No.

**Base-free  $\beta$ -boration of  $\alpha,\beta$ -unsaturated imines catalysed by  $\text{Cu}_2\text{O}$  with concurrent enhancement of asymmetric induction**

The activation of the diboron reagent,  $\text{B}_2\text{pin}_2$ , with  $\text{Cu}_2\text{O}$  does not need external base to form the  $\text{CuBpin}$  moiety. We have demonstrated that  $\text{Cu}_2\text{O}$ -Ligand guarantees the  $\alpha,\beta$ -unsaturated imine formation from chalcone-ketone derivatives, aliphatic cyclic and acyclic ketones, but also efficiently  $\beta$ -borate the  $\alpha,\beta$ -unsaturated imine formed with high values of conversion. The modification of  $\text{Cu}_2\text{O}$  with commercially available chiral ligands, such as (R)-BINAP, enhances the asymmetric induction on the C-B bond formation, principally when the Bn group is attached to the imine. The *in situ* IR spectroscopy shows a clean and rapid pseudo first order reaction for  $\text{Cu}_2\text{O}$ , which is slightly faster for a cyclic enone-derived imine compared with an acyclic substrate.

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# Supporting information

## Base-free $\beta$ -boration of $\alpha,\beta$ -unsaturated imines catalysed by $\text{Cu}_2\text{O}$ with concurrent enhancement of asymmetric induction

Adam D. J. Calow,<sup>[b]</sup> Cristina Solé,<sup>[a]</sup> Andrew Whiting,<sup>\*[b]</sup> Elena Fernández<sup>\*[a]</sup>

### Contents

1. Instrumentation and chemicals.
2. Experimental procedure for copper/(R)-BINAP catalyzed  $\beta$ -boration of  $\alpha,\beta$ -unsaturated imines with bis(pinacolato)diboron.
3. Screening of chiral ligands for the asymmetric  $\text{Cu}_2\text{O}/\text{L}$  catalysed  $\beta$ -boration of  $\alpha,\beta$ -unsaturated imines formed *in situ*.
4. Characterization of  $\beta$ -boryl imines.
5. Analysis of the enantiomeric excess by HPLC.
6. ReactIR
7. References.

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## 1. Instrumentation and chemicals

All reactions and manipulations were carried out under an argon atmosphere by using Schlenk-techniques or Radleys Carousel 12 Reaction. Dry solvents were dried using MBRAUN Solvent Purification System (MB-SPS). Bis(pinacolato)diboron was used as purchased from AllyChem. (*R*)-(*S*)-Mandyphos, (*R*)-(*S*)-Taniphos, (*R*)-Ph-MeOBiphep, (*R*)-(*R*)-Walphos and (*R*)-(*S*)-Josiphos type ligands were kindly supplied by Solvias. The (*R*)-Binap and (*R*)-Tol-Binap ligands were used as purchased from Strem.

All other materials were purchased directly from standard chemical suppliers and used without further purification, unless stated otherwise.

High performance liquid chromatography (HPLC) was carried out using a Shimadzu Class VP model equipped with an autosampler and UV detector or Hewlett-Packard HP 5989 MS at an ionizing voltage of 70 eV. Chiralpak AD-H column (dimensions 250 × 4.6 mm), Chiralpak IA-H column (dimensions 250 × 4.6 mm) were used to determine enantiomeric excesses.

Deuterated chloroform ( $\text{CDCl}_3$ ) was used as solvents for routine NMR measurements. NMR spectra were obtained using a Varian Mercury 400 spectrometer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR chemical shifts are reported in ppm ( $\delta$ ) relative to tetramethylsilane, referenced to the chemical shift of residual solvents resonances.  $^{11}\text{B}$  { $^1\text{H}$ } NMR chemical shifts are reported in ppm ( $\delta$ ) relative to  $\text{BF}_3 \cdot \text{OEt}_2$  ( $\delta$   $^{11}\text{B}$  = 0.00 ppm) as the external reference. Chemical shift values ( $\delta$ ) are given in ppm, coupling constants ( $J$ ) are given in Hz, and NMR peaks are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).

## 2. Experimental procedure for copper/(R)-BINAP catalysed $\beta$ -boration of $\alpha,\beta$ -unsaturated imines with bis(pinacolato)diboron.

Copper(I) salts (1.5-3 mol%), (R)-BINAP ligand (3-6 mol%, 0.0075-0.015 mmol, 4.7-9.3 mg), were transferred into a Schlenk tube and dissolved in THF (1 mL) under Ar. After 15 min, bis(pinacolato)diboron (70 mg, 0.28 mmol, 1.1 equiv.) was added to the solution and stirred during 10 min. Then benzylamine (0.25 mmol, 27  $\mu$ l) and 4-phenyl-3-buten-2-one (**1**) (0.25 mmol, 36.5 mg) were added at the same time (or the corresponding isolated (*E*)-1-phenyl-N-(4-phenylbutan-2-ylidene)methanamine (**4a**)<sup>1</sup> (0.25 mmol, 59 mg)), followed by the addition of MeOH (0.55 mmol, 25  $\mu$ l, 2.5 equiv.). The reaction mixture was stirred overnight at RT. The reaction products and conversion to the desired  $\beta$ -boryl imine was determined by <sup>1</sup>H NMR and the enantiomeric excess was determined directly by HPLC-UV.

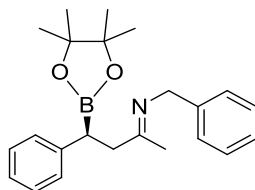
## 3. Screening of chiral ligands for the asymmetric Cu<sub>2</sub>O/L catalysed $\beta$ -boration of $\alpha,\beta$ -unsaturated imines formed *in situ*.

Cu<sub>2</sub>O (3 mol%, 0.0075 mmol, 1 mg), chiral diphosphine (6 mol%, 0.015 mmol) and THF (1 mL) were transferred into a Radley's Carousel 12 place reactor under Ar. The mixture was stirred for 15 min at room temperature. Bis(pinacolato)diboron (0.28 mmol, 70 mg, 1.1 equiv.) was added and the solution was stirred for 10 min. Then benzylamine (0.25 mmol, 27  $\mu$ l, 1 equiv.) and the  $\alpha,\beta$ -unsaturated ketone (0.25 mmol) were added simultaneously, followed by the addition of MeOH (0.55 mmol, 25  $\mu$ l, 2.5 equiv.). The reaction mixture was stirred overnight at RT. The products obtained were analyzed by <sup>1</sup>H NMR spectroscopy to determine the conversion towards the desired  $\beta$ -boryl imine products. The enantiomeric excess of **3a**, **6** and **8**, were determined directly by HPLC-UV, otherwise, the enantiomeric excess of the other  $\beta$ -boryl imines **3b**, **10**, **12**, **14**, **16** was determined by HPLC-MS from the corresponding  $\beta$ -boryl ketone derivative obtained by hydrolysis. Purification was carried out by silica gel column chromatography (see below in section 4).

*The hydrolysis protocol:* To determine enantiomeric excesses of the  $\beta$ -boration products, some of the  $\beta$ -boryl imines obtained in the above procedures were converted into the corresponding  $\beta$ -boryl ketones following the procedure: Distillated water (1 mL) was added to the crude reaction product (cc. 0.25 mmol) in THF (1 mL). The reaction mixture was stirred vigorously for 2 h at RT. Then diluted with dichloromethane and extracted (3 x 2 mL). The combined organic phases were dried over Mg<sub>2</sub>SO<sub>4</sub> and concentrated. The  $\beta$ -boryl ketones derived were dissolved in isopropanol solvent and analysed by chiral HPLC-MS to determine the enantiomeric excess.

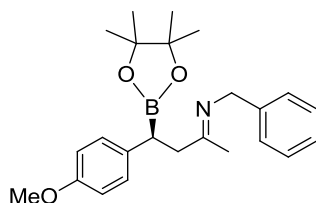
## 4. Characterization of $\beta$ -boryl imines.

### 4.1 Synthesis of (S,E)-1-phenyl-N-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)methanamine (3a)



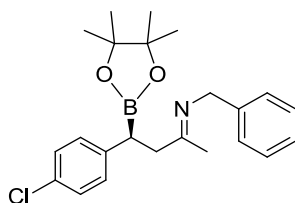
Using the procedure described in section 3 and (*R*)-BINAP as ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:1, 10% anhydrous triethylamine); isolated yield 90%;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.37 – 7.26 (m, 4H), 7.24–7.11 (m, 5H), 7.05 (t,  $J$  = 7.2 Hz, 1H), 4.86 (d,  $J$  = 15.2 Hz, 1H), 4.72 (d,  $J$  = 15.2 Hz, 1H), 3.09 (dd,  $J$  = 19.6, 8 Hz, 1H), 2.89 (dd,  $J$  = 19.6, 8 Hz, 1H), 2.33 (t,  $J$  = 8 Hz, 1H), 1.99 (s, 3H), 0.99 (s, 6H), 0.87 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  189.9, 146.7, 135.9, 128.7, 128.1, 127.7, 127.6, 127.4, 123.8, 79.63, 49.5, 26.9, 26.3, 24.6, 19.3.  $^{11}\text{B}$  NMR ( $\text{CDCl}_3$ , 128.3 MHz)  $\delta$  21.2. MS  $m/z$  (ESI+) 364.24 ( $M+1$ ). The spectroscopic data match those reported previously.<sup>2,3</sup>

### 4.2 Synthesis of (S,E)-N-(4-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine (6)



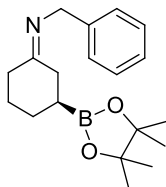
Using the procedure described in section 3 and (*R*)-BINAP as ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:1, 10% anhydrous triethylamine); isolated yield 45%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38–7.28 (m, 5H), 7.12 (d,  $J$  = 8.4 Hz, 2H), 6.79 (d,  $J$  = 8.4 Hz, 2H), 4.86 (d,  $J$  = 14.8 Hz, 1H), 4.73 (d,  $J$  = 14.8 Hz, 1H), 3.75 (s, 3H), 3.05 (dd,  $J$  = 19.6, 8.4 Hz, 1H), 2.83 (dd,  $J$  = 19.6, 8.4 Hz, 1H), 2.27 (t,  $J$  = 8 Hz, 1H), 1.99 (s, 3H), 0.99 (s, 6H), 0.90 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  184.53, 156.42, 138.72, 135.97, 129.09, 128.81, 127.66, 127.36, 113.90, 113.09, 79.59, 55.21, 49.45, 46.53, 27.01, 26.34, 24.81, 19.32;  $^{11}\text{B}$  NMR ( $\text{CDCl}_3$ , 128.3 MHz)  $\delta$  19.21. MS  $m/z$  (ESI+) 394.25 ( $M+1$ ). The spectroscopic data match those reported previously.<sup>3</sup>

#### 4.3 Synthesis of (S,E)-N-(4-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine (8)



Using the procedure described in section 3 and (*R*)-BINAP as a ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:1, 10% anhydrous triethylamine); isolated yield 87%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 – 7.27 (m, 5H), 7.15 (d,  $J$  = 8.4 ,2H), 7.06 (d,  $J$  = 8.4, 2H), 4.84 (d,  $J$  = 15.2 Hz, 1H), 4.72 (d,  $J$  = 15.2 Hz, 1H), 2.99 (dd,  $J$  = 20.4, 8 Hz, 1H), 2.79 (dd,  $J$  = 20.4, 8 Hz, 1H), 2.29 (t,  $J$  = 8 Hz, 1H), 1.99 (s, 3H), 0.97 (s, 6H), 0.87 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  189.84, 145.27, 135.75, 129.52, 129.36, 128.78, 128.58, 127.63, 127.56, 127.43, 79.72, 49.49, 26.97, 26.32, 24.57, 19.29.  $^{11}\text{B}$  NMR ( $\text{CDCl}_3$ , 128.3 MHz)  $\delta$  18.93. MS  $m/z$  (ESI+) 398.19 ( $M+1$ ). The spectroscopic data match those reported previously.<sup>3</sup>

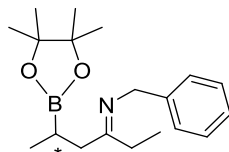
#### 4.4 Synthesis of (S,Z)-1-phenyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexylidene)methanamine (10)



Using the procedure described in section 3 and (*R*)-BINAP as ligand, the title compound was isolated as an colorless oil by chromatography (dry silica, DCM:hexane v:v =1:3, 10% anhydrous triethylamine); isolated yield 89%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 – 7.20 (m, 5H), 4.59 (m, 2H), 2.35 – 2.17 (m, 4H), 1.72 – 1.51 (m, 2H), 1.69 – 1.49 (m, 2H), 1.45 – 1.29 (m, 1H), 1.24 (s, 12H);  $^{13}\text{C}$  NMR (75.4 MHz,  $\text{CDCl}_3$ )  $\delta$  189.80, 136.76, 128.60, 127.47, 114.20, 78.98, 54.82, 48.85, 43.70, 26.77, 24.84, 24.69, 17.60;  $^{11}\text{B}$  NMR ( $\text{CDCl}_3$ , 128.3 MHz)  $\delta$  22.15. MS  $m/z$  (ESI+) 314.24 ( $M+1$ ) .

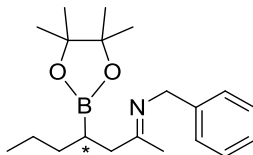


#### 4.5 Synthesis of (E)-1-phenyl-N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-ylidene)methanamine (12)



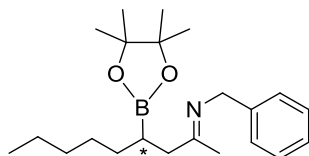
Using the procedure described in section 3 and (*R*)-BINAP as a ligand, the title compound was isolated as an pale yellow oil by chromatography (dry silica, DCM:hexane v:v =1:2, 10% anhydrous triethylamine); isolated yield 35%;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.38 – 7.27 (m, 2H), 7.25 – 7.19 (m, 2H), 7.18 – 7.05 (m, 1H), 4.73 (d,  $J$  = 15.2 Hz, 1H), 4.58 (d,  $J$  = 15.2 Hz, 1H), 2.93 (dd,  $J$  = 22.4, 6.8 Hz 1H), 2.47 (t,  $J$  = 7.6 Hz, 1H), 2.19 (q,  $J$  = 7.6 Hz, 2H), 2.09 (dd,  $J$  = 22.4, 3.5 Hz, 1H), 1.25 (d,  $J$  = 7.6 Hz, 3H), 1.13(s, 6H), 1.09 (s, 6H), 0.81 (t,  $J$  = 7.6 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  189.80, 136.76, 128.60, 127.47, 114.20, 78.98, 48.85, 43.70, 26.77, 24.84, 17.60, 9.26.  $^{11}\text{B}$  NMR ( $\text{CDCl}_3$ , 128.3 MHz)  $\delta$  13.83. MS  $m/z$  (ESI+) 316.25 ( $M+1$ ).

#### 4.6 Synthesis of (E)-1-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-ylidene)methanamine (14)

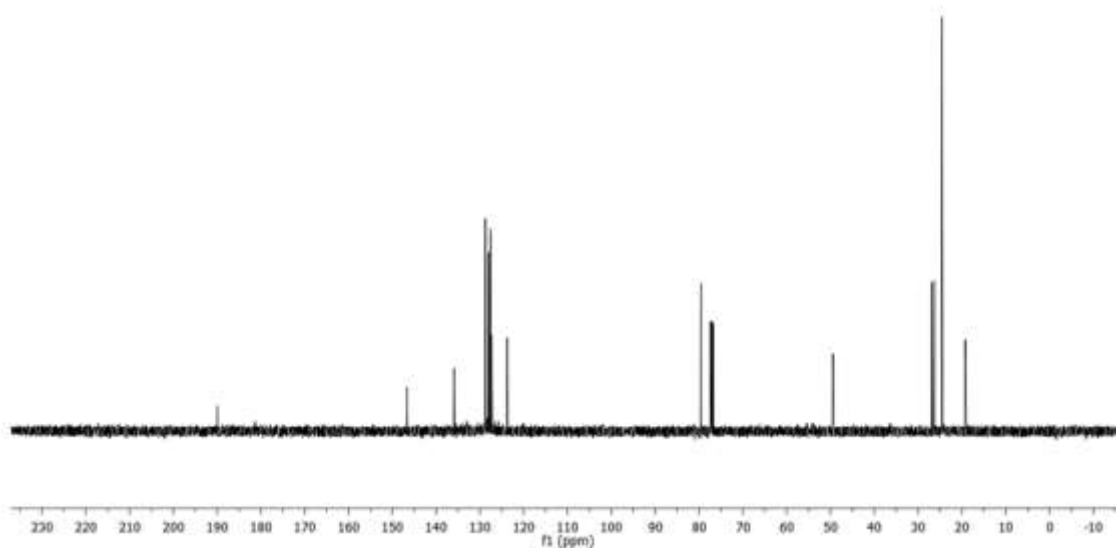
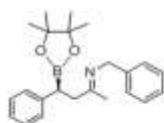
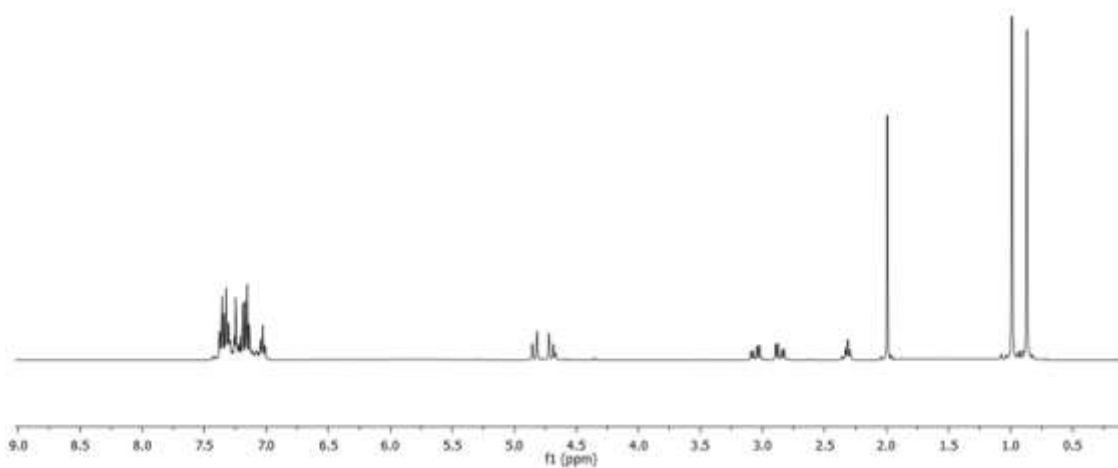
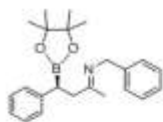


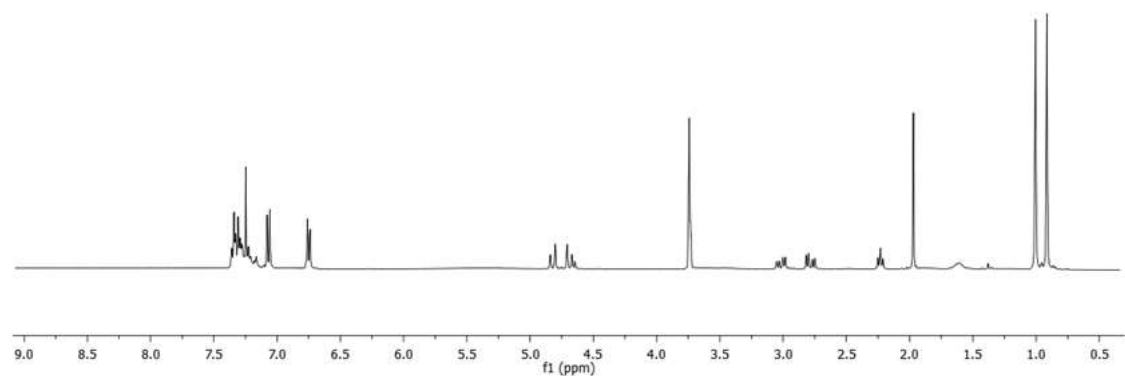
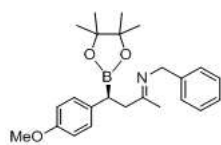
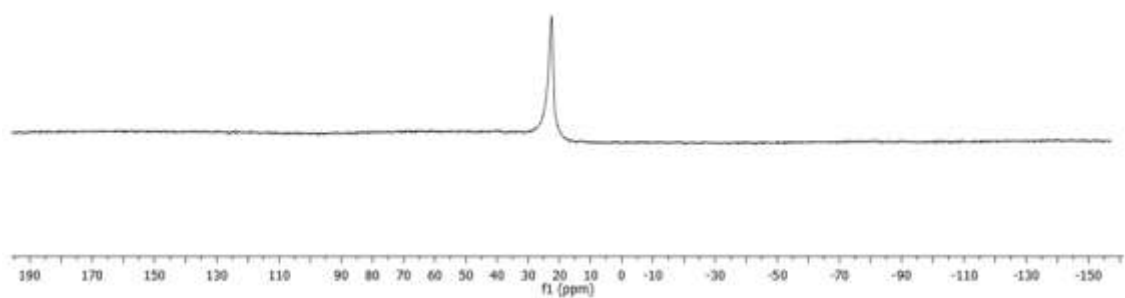
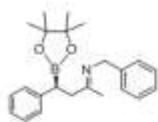
Using the procedure described in section 3 and (*R*)-BINAP as ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:2, 10% anhydrous triethylamine); isolated yield 63%;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.29 – 7.23 (m, 4H), 7.18 – 7.15 (m, 1H), 4.71 (d,  $J$  = 15.2 Hz, 1H), 4.60 (d,  $J$  = 15.2 Hz, 1H), 2.74 (m, 1H), 2.48 (t,  $J$  = 6.6 Hz, 1H), 2.19 (dd,  $J$  = 19.7, 3.5 Hz, 1H), 1.84 (s, 3H), 1.52-1.34 (m, 2H), 1.29-1.23 (m, 2H), 1.13 (s, 6H), 1.10 (s, 6H), 0.82 (t,  $J$  = 7.3 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  189.86, 143.18, 136.25, 128.64, 128.52, 128.36, 128.15, 128.01, 127.54, 127.16, 127.05, 126.78, 79.05, 46.46, 34.43, 27.00, 26.42, 24.83, 22.83, 19.29, 14.36.  $^{11}\text{B}$  NMR ( $\text{CDCl}_3$ , 128.3 MHz)  $\delta$  13.99. MS  $m/z$  (ESI+) 329.25 ( $M+1$ ).

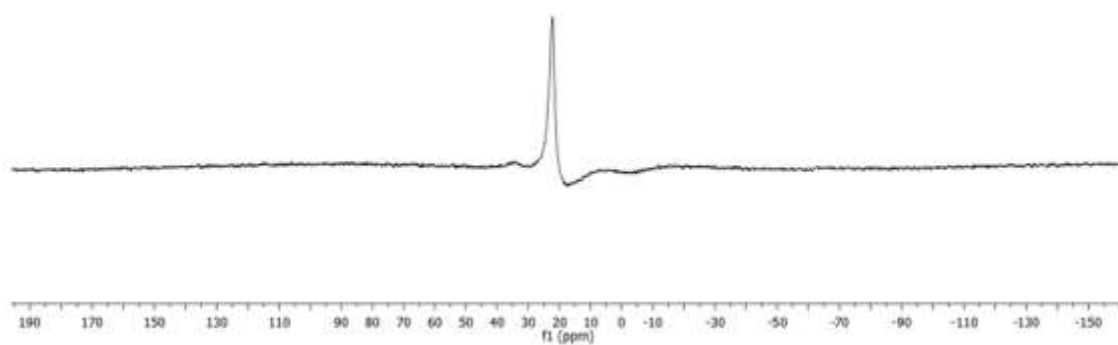
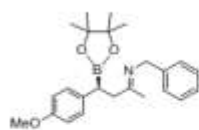
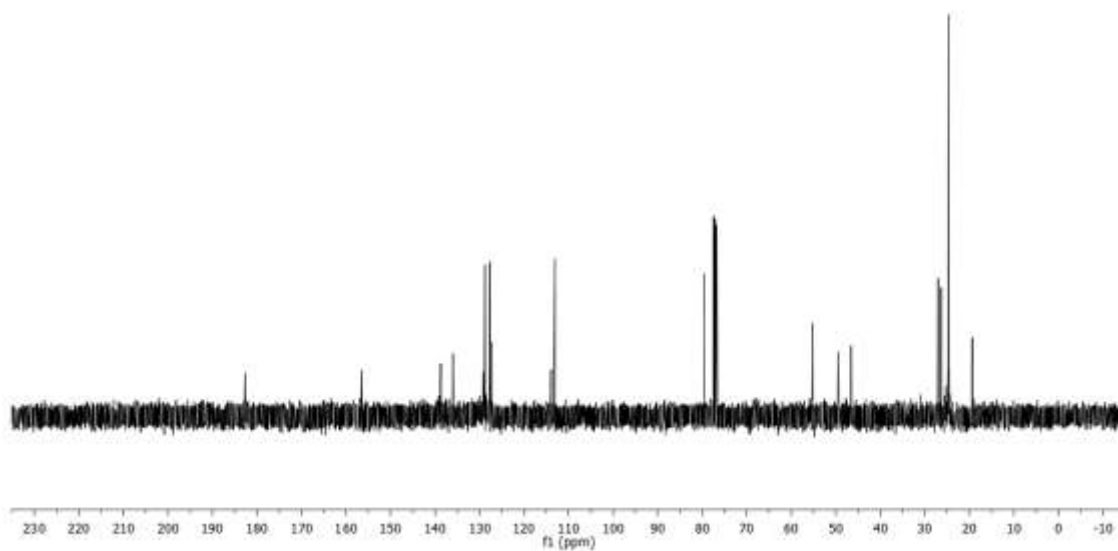
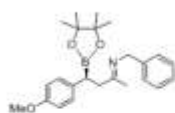
#### 4.7 Synthesis of (E)-1-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-ylidene)methanamine (16)

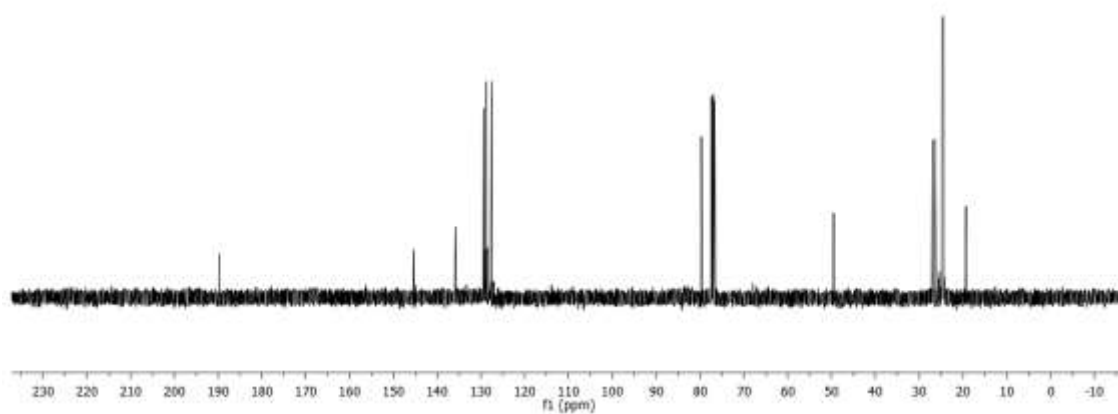
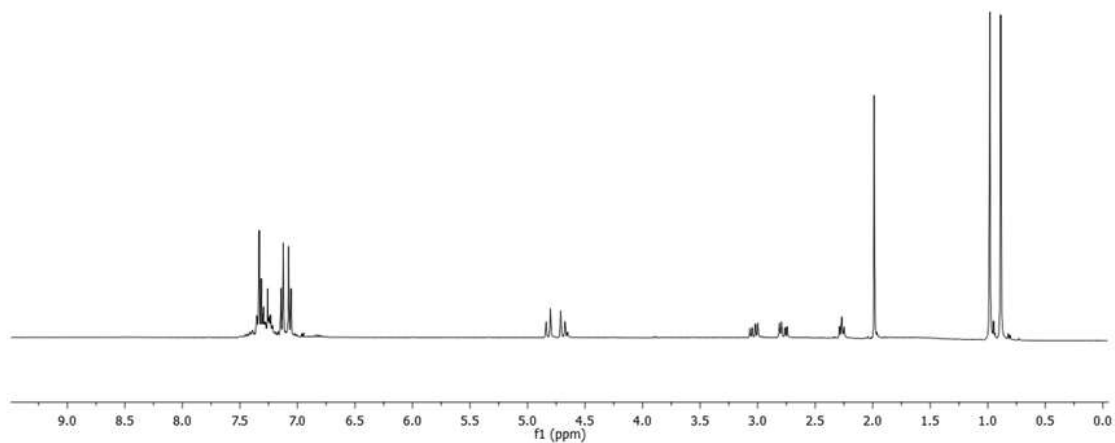


Using the procedure described in section 3 and (*R*)-BINAP as ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:2, 10% anhydrous triethylamine); isolated yield 56%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.25 (m, 4H), 7.18-7.16 (m, 1H), 4.71 (d,  $J$  = 15.2 Hz, 1H), 4.59 (d,  $J$  = 15.2 Hz, 1H), 2.74 (dd,  $J$  = 19.7, 8.0 Hz, 1H), 2.46 (t,  $J$  = 6.6 Hz, 1H), 2.26 (dd,  $J$  = 19.7, 3.5 Hz, 1H), 1.81 (s, 3H), 1.63-1.56 (m, 2H), 1.29-1.18 (m, 6H), 1.14 (s, 6H), 1.10 (s, 6H), 0.87 (t,  $J$  = 6.4 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.6 MHz)  $\delta$  189.79, 143.25, 136.27, 128.63, 128.50, 128.35, 128.14, 128.01, 127.55, 127.15, 127.03, 126.87, 126.75, 79.03, 46.49, 32.13, 29.66, 27.02, 25.28, 24.73, 22.81, 19.28, 14.18;  $^{11}\text{B}$  NMR ( $\text{CDCl}_3$ , 128.3 MHz)  $\delta$  14.26. MS  $m/z$  (ESI+) 357.20 ( $M+1$ )

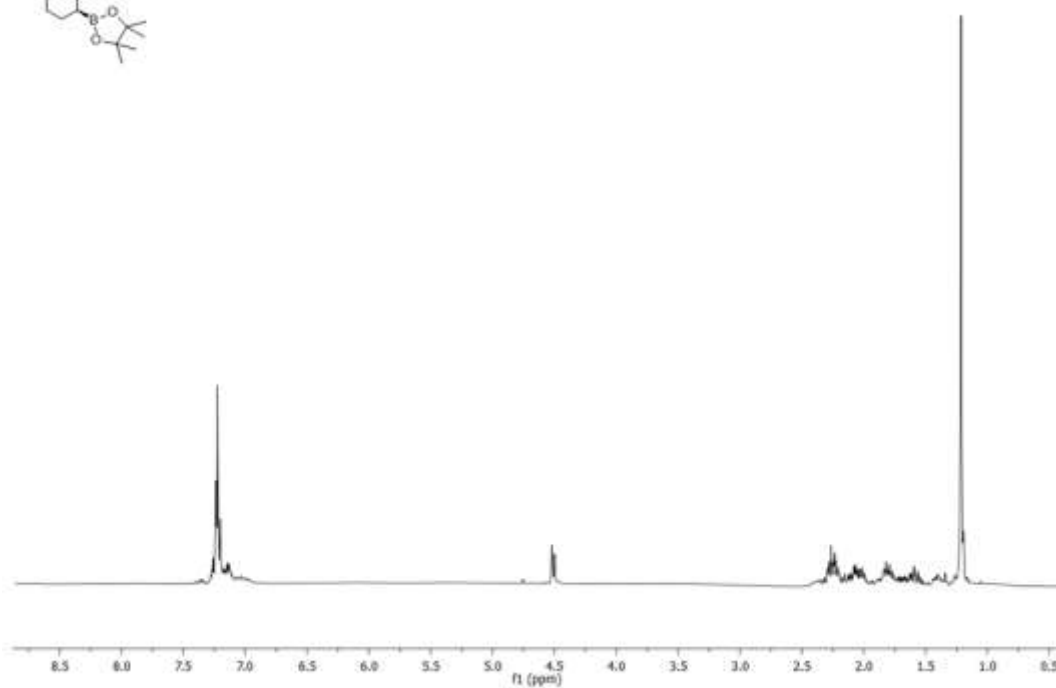
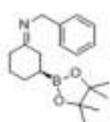
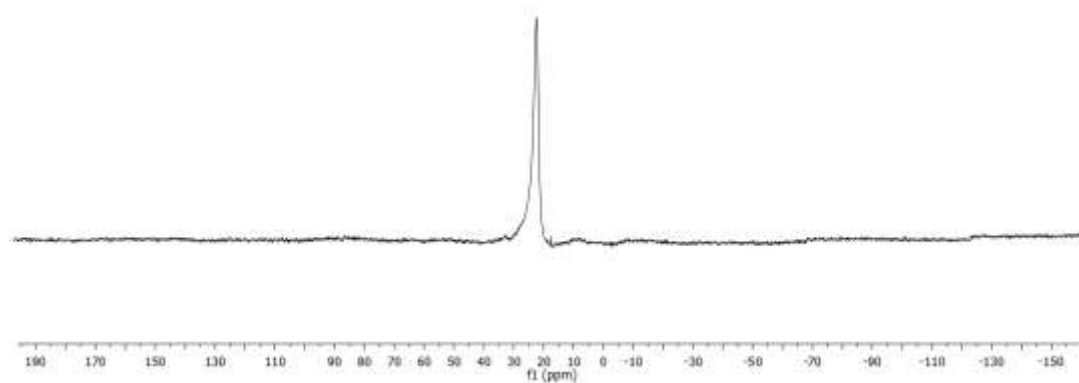
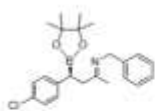


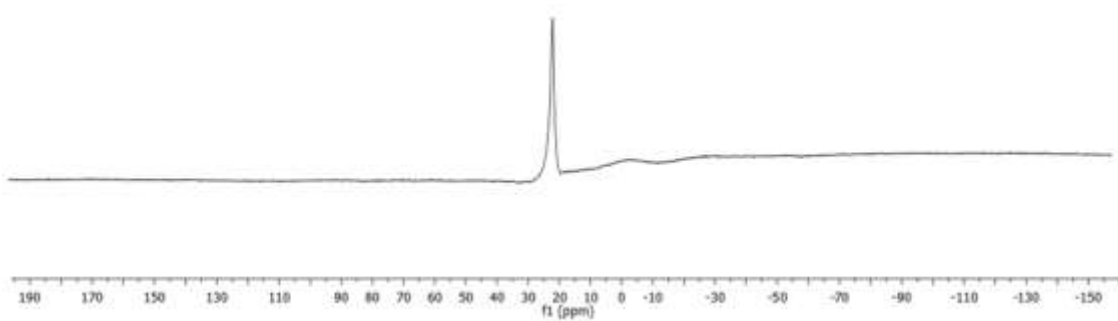
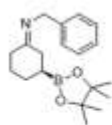
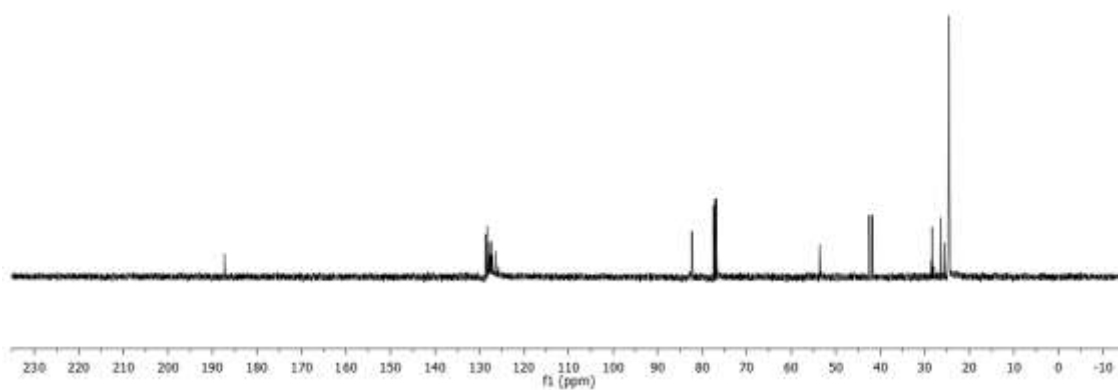
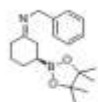


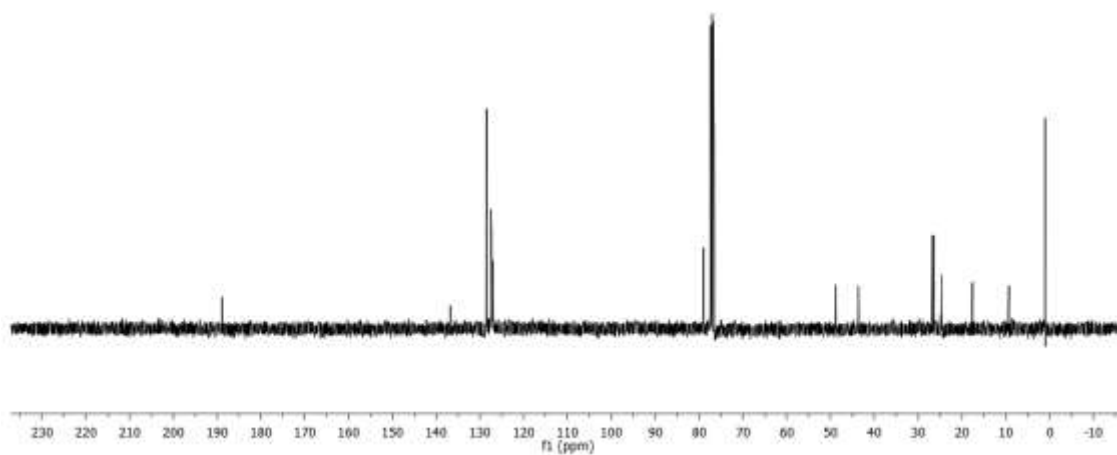
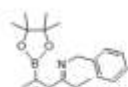
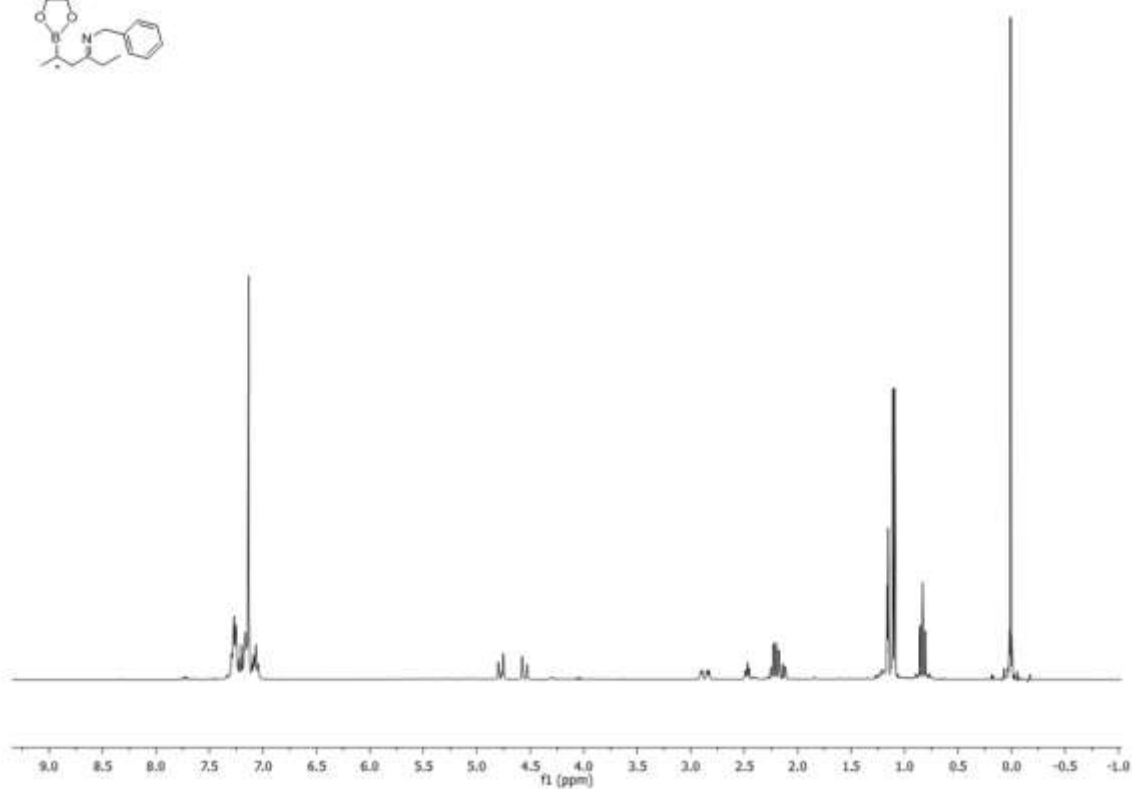
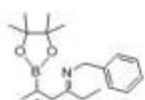


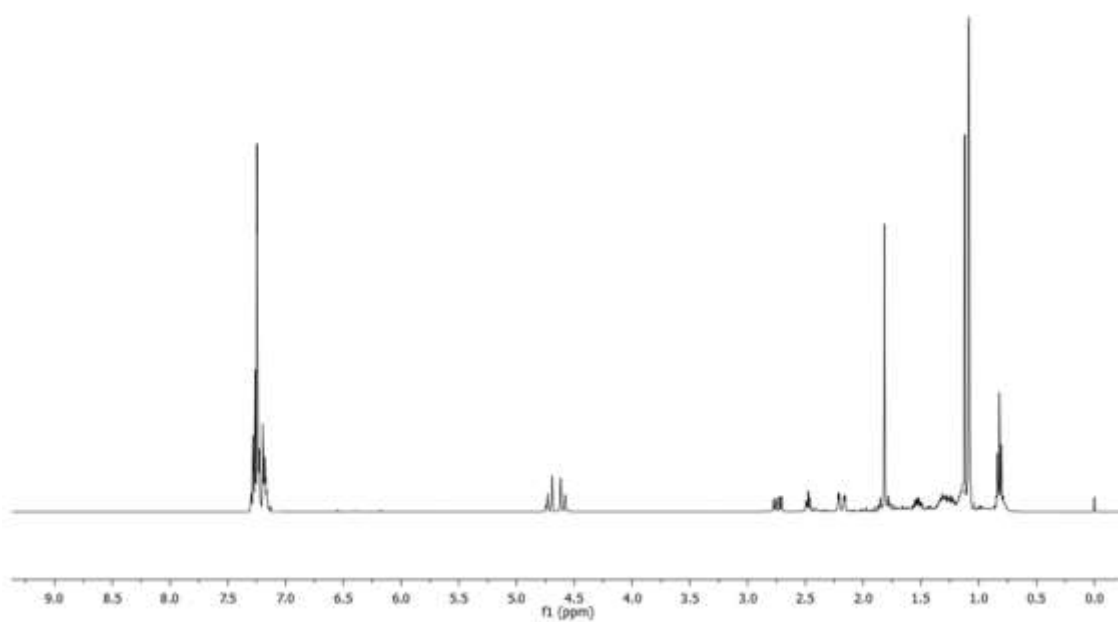
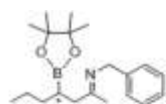
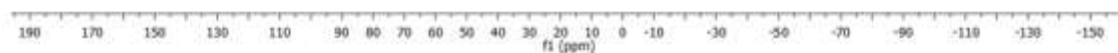
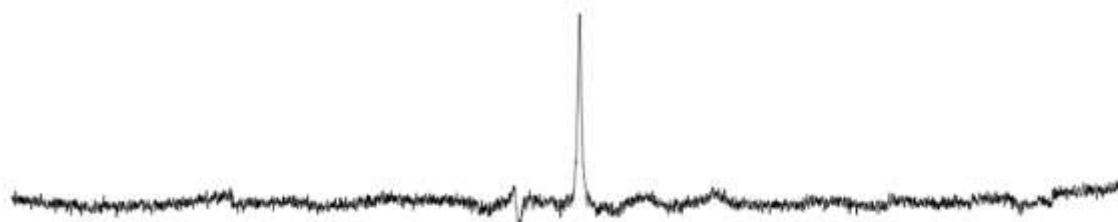
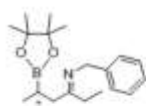


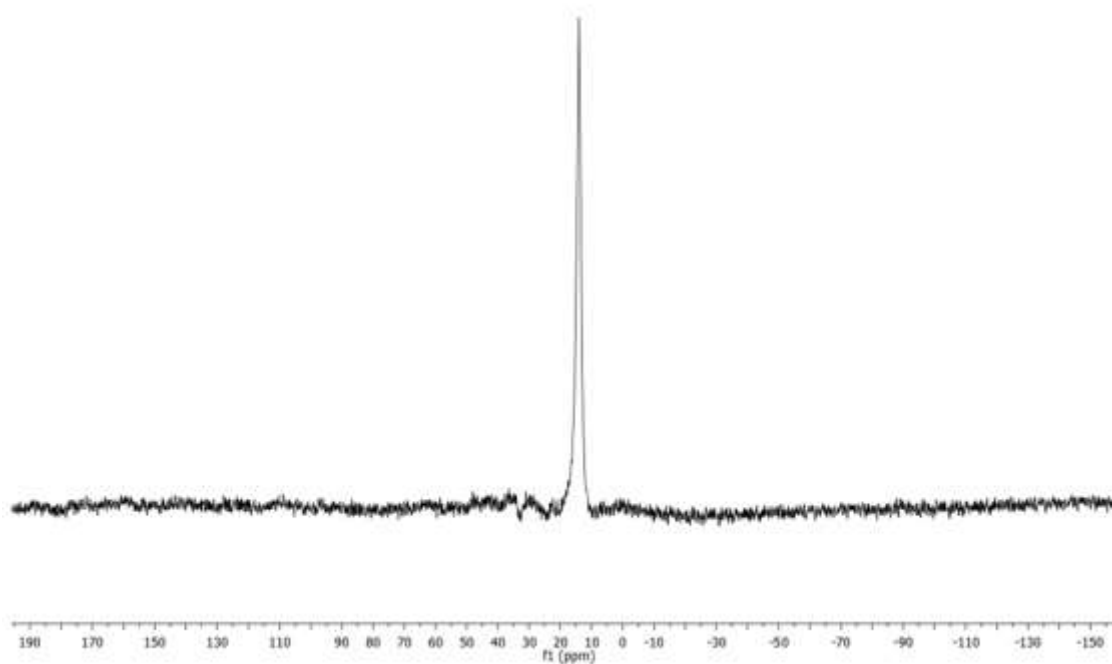
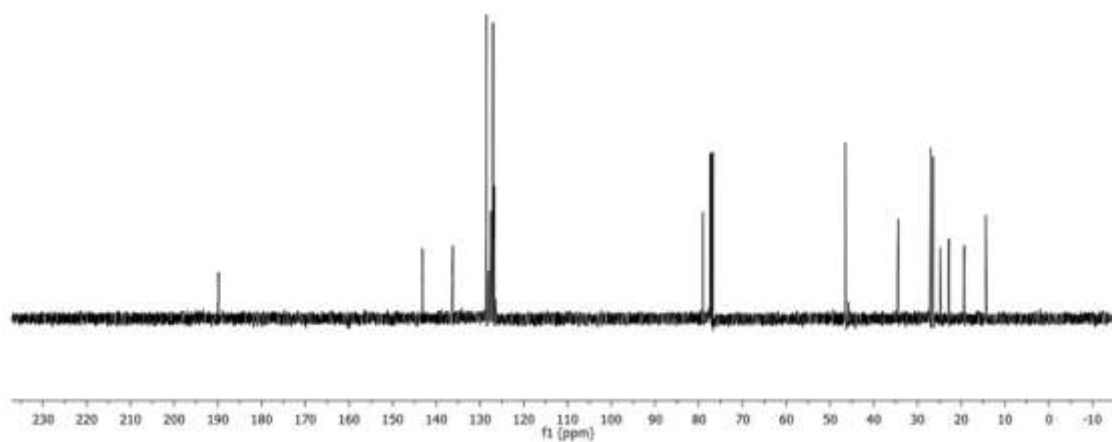


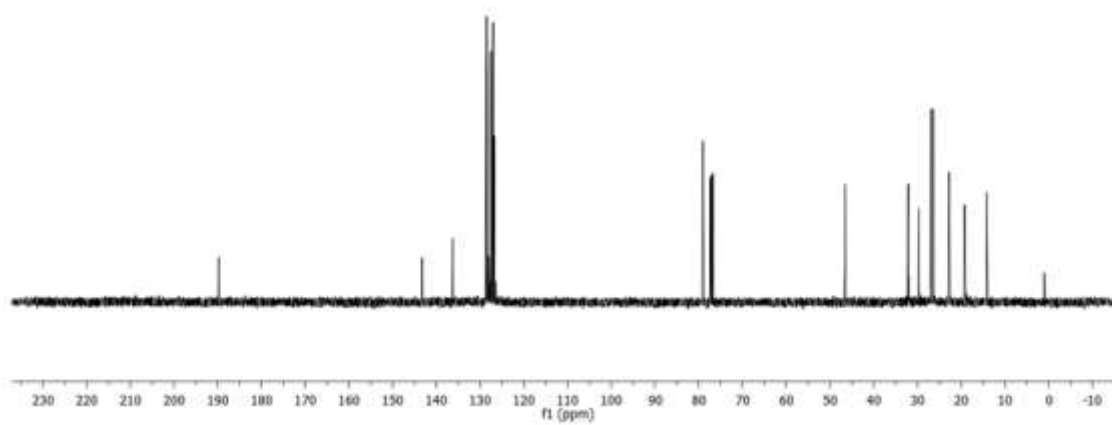
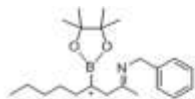
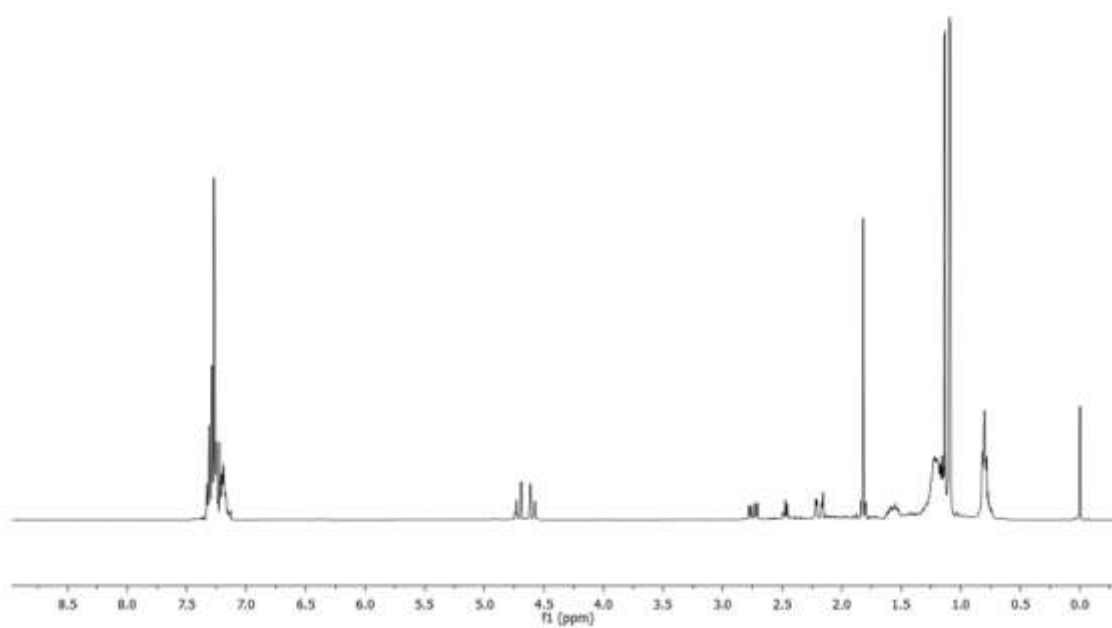
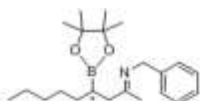




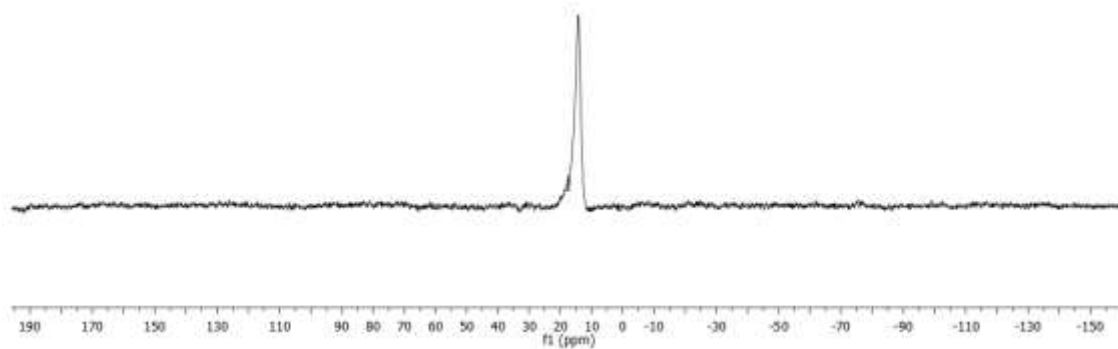
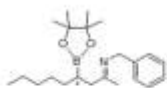






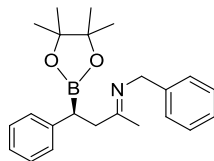






## 5. Analysis of the enantiomeric excess by HPLC.

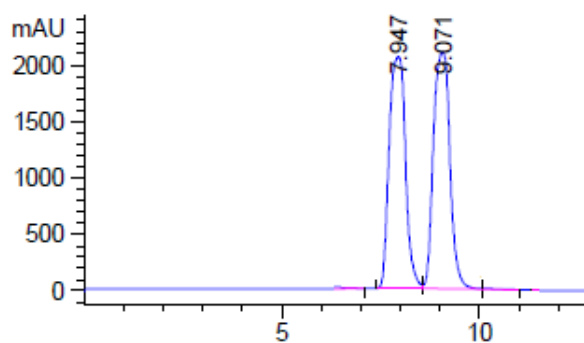
### 5.1 Analysis of (*S,E*)-1-phenyl-N-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)methanamine (**3a**)



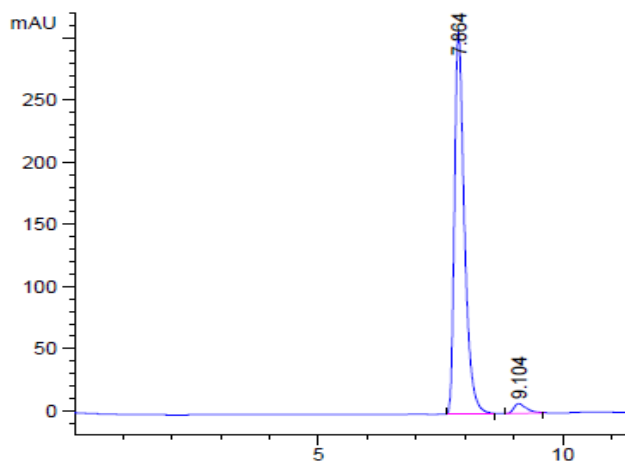
The enantiomeric excess were obtained by chiral HPLC analysis of **3a** using an AD-H column (iPrOH-hexane, 95:5, 1mL/min, UV detection at 254 nm); (*S*)-isomer  $t_r$ = 7.9min and (*R*)-isomer  $t_r$ = 9.1min. Specific rotation of **3a**:  $[\alpha]_D^{25} +40.9$  (c 0.95 in  $\text{CHCl}_3$  for a (*S*)-enantiomerically enriched sample of 93ee%).

The absolute configuration was assigned by comparison of the optical rotation of the corresponding  $\beta$ -borated ketone compound obtained after hydrolysis of the boronate product:  $[\alpha]_D^{25} +34.6$  (c 1.02 in  $\text{CHCl}_3$ ). Value found in the literature<sup>i</sup>:  $[\alpha]_D^{20} -34.2$  (c 1.06,  $\text{CHCl}_3$  for a (*R*)-enantiomerically enriched sample of 96:4 er).

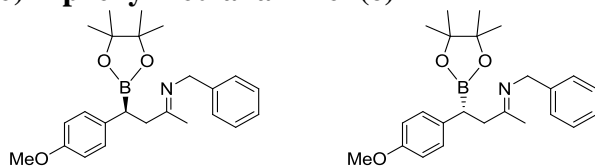
*Racemic*



*95% ee*



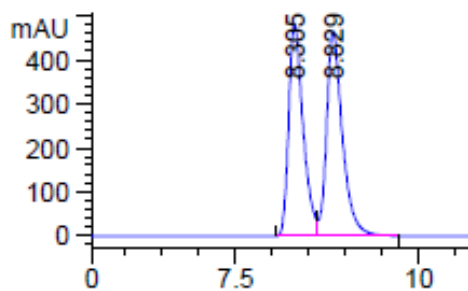
## 5.2 Analysis of (*S* or *R,E*)-*N*-(4-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine (**6**)



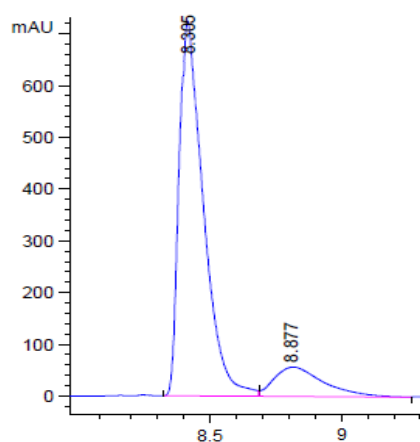
The enantiomeric excess were obtained by chiral HPLC analysis of **6** using an AD-H column (iPrOH-hexane, 97:3, 1mL/min, UV detection at 254 nm); (*S*)-isomer  $t_r$  = 8.3min and (*R*)-isomer  $t_r$  = 8.9min. Specific rotation of **6**:  $[\alpha]_D^{25}$  +52.5 (c 1.08 in  $\text{CHCl}_3$  for a (*S*)-enantiomerically enriched sample of 86ee%) and  $[\alpha]_D^{25}$  -26.6 (c 1.00 in  $\text{CHCl}_3$  for a (*R*)-enantiomerically enriched sample of 49ee%)

The absolute configuration was assigned by comparison of the optical rotation of the corresponding  $\beta$ -borated ketone compound obtained after hydrolysis of the boronate product:  $[\alpha]_D^{25}$  +36.1 (c 0.70 in  $\text{CHCl}_3$ ). Value found in the literature<sup>1</sup>:  $[\alpha]_D^{20}$  -29.1 (c 1.07,  $\text{CHCl}_3$  for a (*R*)-enantiomerically enriched sample of 96:4 er).

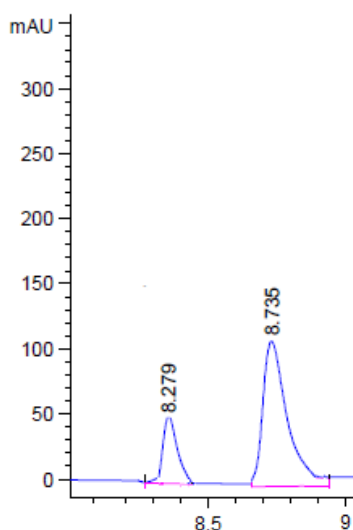
*Racemic*



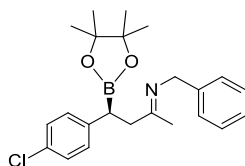
*86% ee of (S)-isomer*



*49% ee of (R)-isomer*



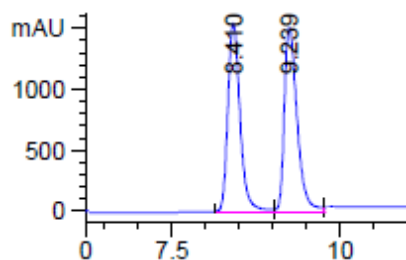
### 5.3 Analysis of (*S,E*)-*N*-(4-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine (**8**)



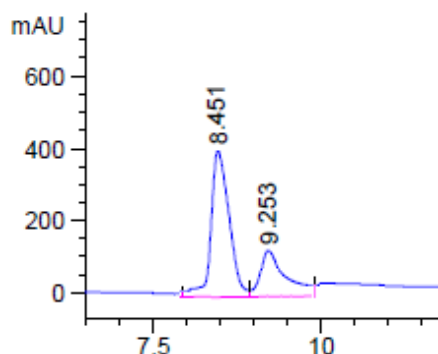
The enantiomeric excess were obtained by chiral HPLC analysis of **8** using an AD-H column (iPrOH-hexane, 99:1, 1mL/min, UV detection at 254 nm); (*S*)-isomer  $t_r$  = 8.4min and (*R*)-isomer  $t_r$  = 9.2min. Specific rotation of **8**:  $[\alpha]_D^{25} +18.02$  (c 0.88 in CHCl<sub>3</sub> CHCl<sub>3</sub> for a (*S*)-enantiomerically enriched sample of 48ee%) and  $[\alpha]_D^{25} +30.8$  (c 1.5 in CHCl<sub>3</sub> for a (*S*)-enantiomerically enriched sample of 58ee%).

The absolute configuration was assigned by comparison of the optical rotation of the corresponding  $\beta$ -borated ketone compound obtained after hydrolysis of the boronate product:  $[\alpha]_D^{25} +27.5$  (c 0.80 in CHCl<sub>3</sub>). Value found in the literature<sup>i</sup>:  $[\alpha]_D^{20} -12.0$  (c 0.12, CHCl<sub>3</sub> for a (*R*)-enantiomerically enriched sample of 95:5 er).

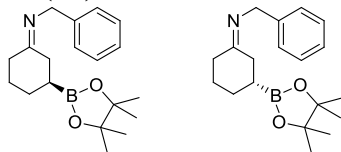
*Racemic*



*58% ee*

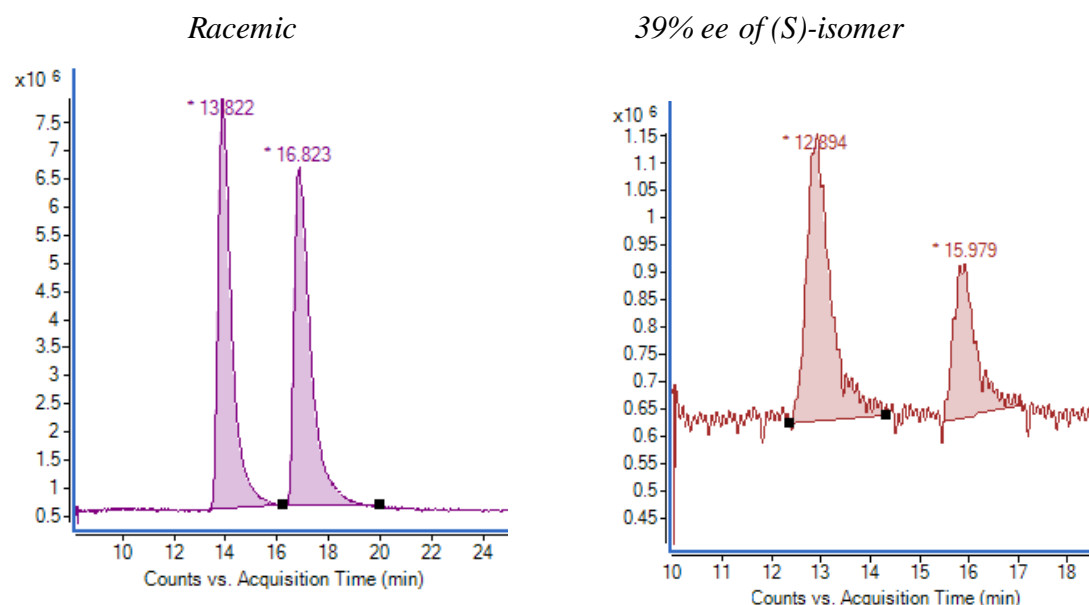


#### 5.4 Analysis of (*S* or *R,Z*)-1-phenyl-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexylidene)methanamine (**10**)

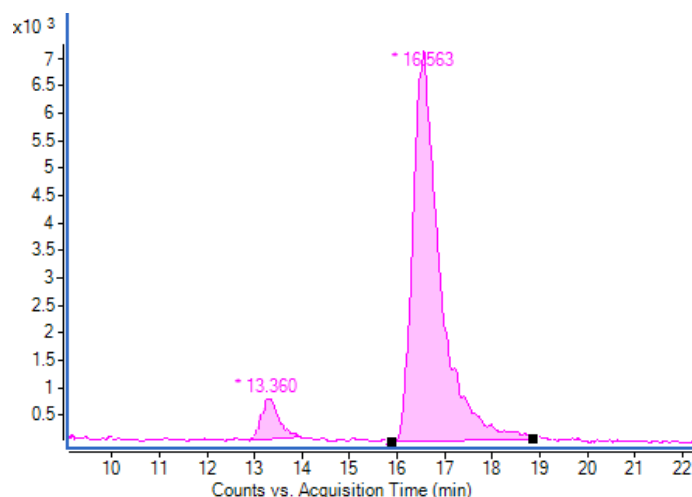


The enantiomeric excess were obtained by chiral HPLC analysis of the corresponding hydrolysed product ((*R*)-4-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one) using an IA-H column (iPrOH-hexane, 0.5:99.5, 1mL/min, HPLC-MS); (*S*)-isomer  $t_r$ =13.8min and (*R*)-isomer  $t_r$ =16.8min. Specific rotation:  $[\alpha]_D^{23}$  -2.5 (c 1.07 in  $\text{CHCl}_3$  for a (*S*)-enantiomerically enriched sample of 39ee%).

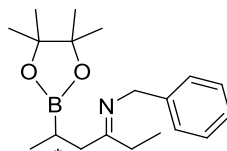
The absolute configuration was assigned by comparison of the optical rotation of the corresponding  $\beta$ -borated ketone compound obtained after hydrolysis of the boronate product:  $[\alpha]_D^{25}$  -4.4 (c 0.50 in  $\text{CHCl}_3$ ). Value found in the literature:<sup>4</sup>  $[\alpha]_D^{20}$  +6.2 (c 1.29,  $\text{CHCl}_3$  for a (*R*)-enantiomerically enriched sample of 83:17 er).



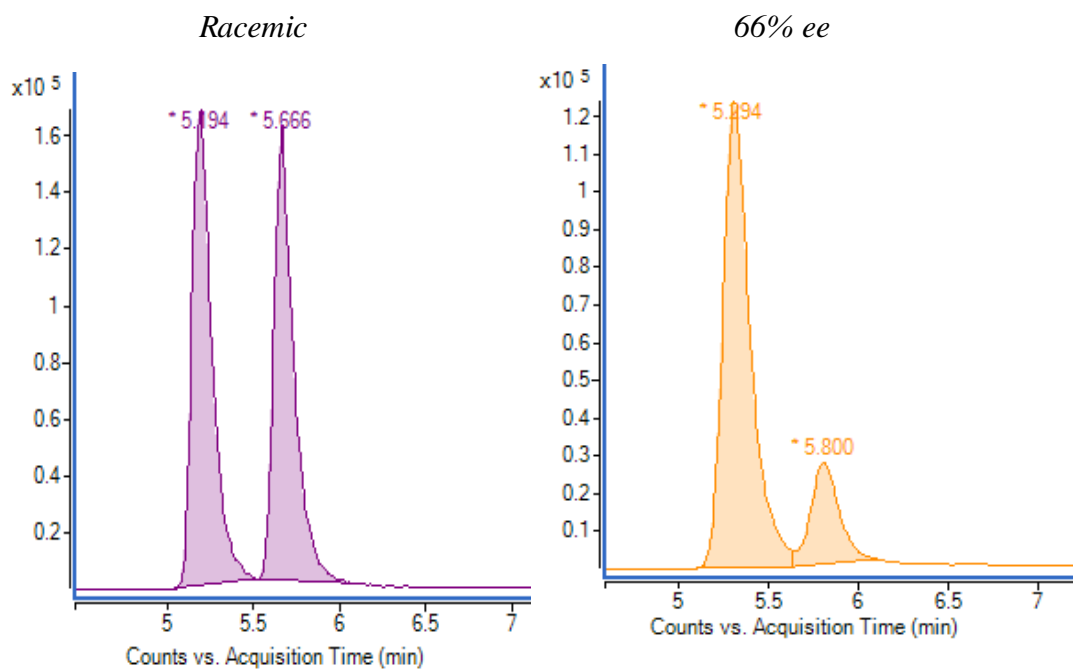
92% ee of (*R*)-isomer



### 5.5 Analysis of (E)-1-phenyl-N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-ylidene)methanamine (12)

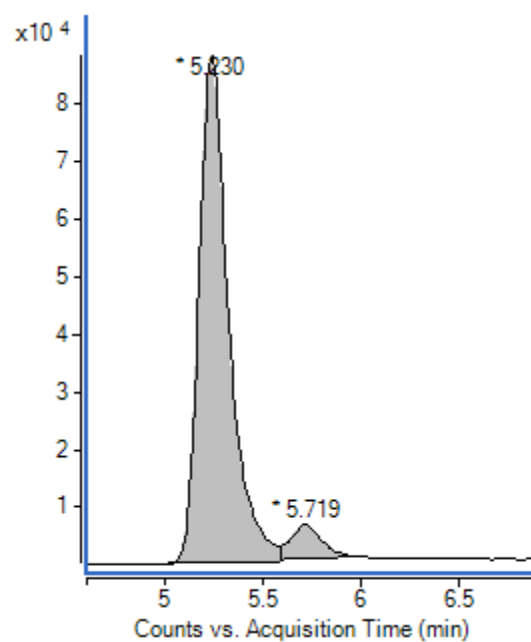


The enantiomeric excess were obtained by chiral HPLC analysis of the corresponding hydrolysed product (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one) using an IA-H column (iPrOH-hexane, 0.5:99.5, 1mL/min, HPLC-MS); the major isomer  $t_r = 5.29$  min and the minor isomer  $t_r = 5.7$  min. Specific rotation:  $[\alpha]_D^{23} +49.7$  (c 1.00 in  $\text{CHCl}_3$  for a sample of 66ee%) and  $[\alpha]_D^{25} +35.7$  (c 0.53 in  $\text{CHCl}_3$  for a sample of 50ee%).

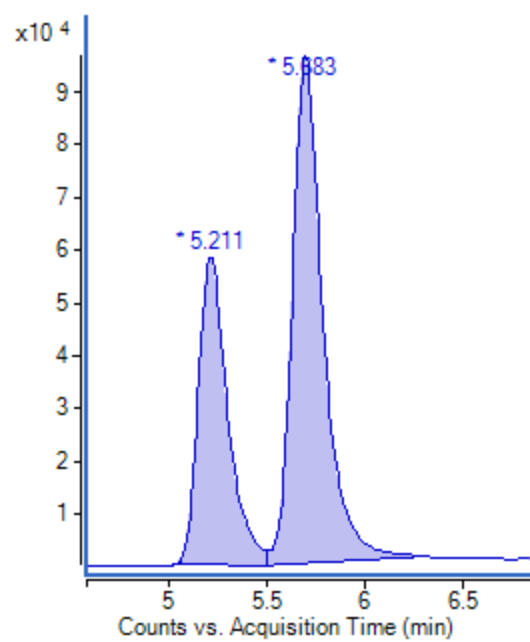




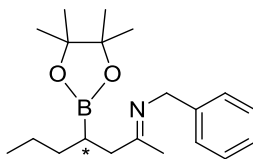
88% ee



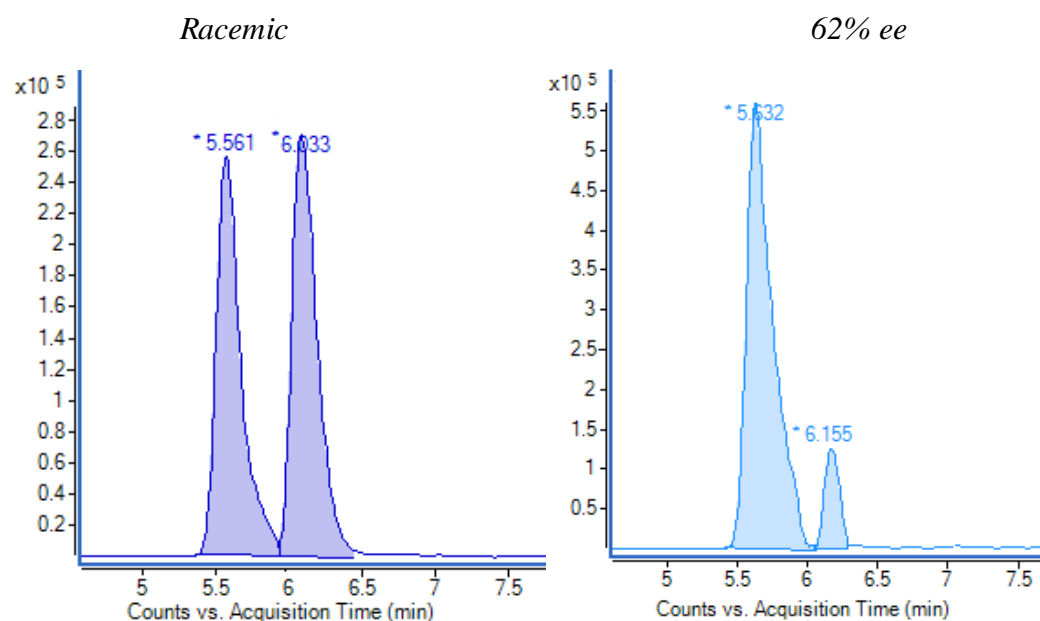
26% ee (other enantiomer)



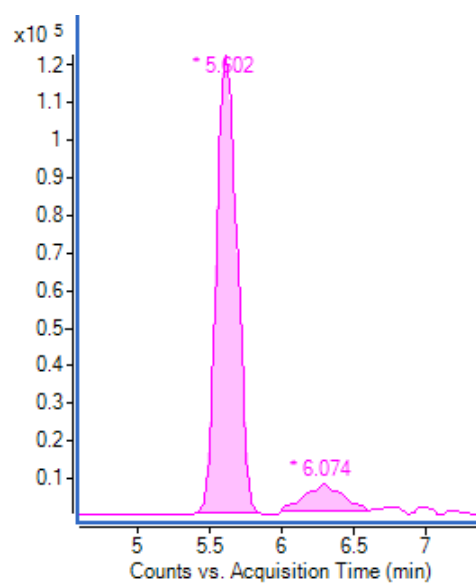
## 5.6 Analysis of (E)-1-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-ylidene)methanamine (14)



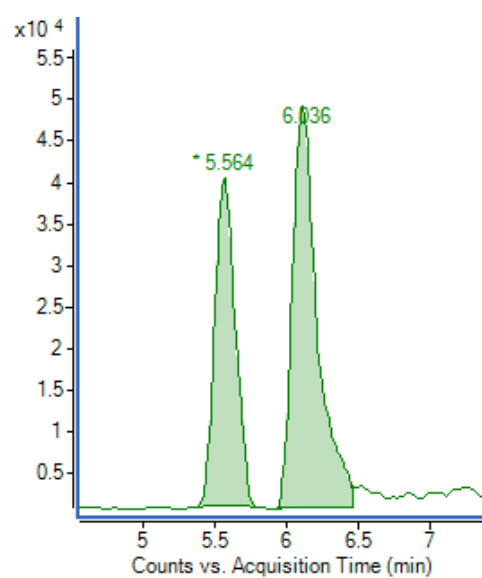
The enantiomeric excess were obtained by chiral HPLC analysis of the corresponding hydrolysed product (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-one) using an IA-H column (iPrOH-hexane, 0.5:99.5, 1mL/min, HPLC-MS); the major isomer  $t_r = 5.56$  min and the minor isomer  $t_r = 6.1$  min. Specific rotation:  $[\alpha]_D^{23} +45.5$  (c 1.3 in  $\text{CHCl}_3$  for a sample of 62ee%) and  $[\alpha]_D^{25} +48.4$  (c 1.3 in  $\text{CHCl}_3$  for a sample of 64ee%).



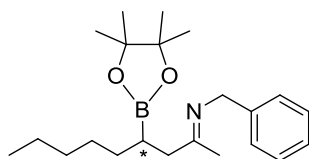
86% ee



10% ee (other enantiomer)



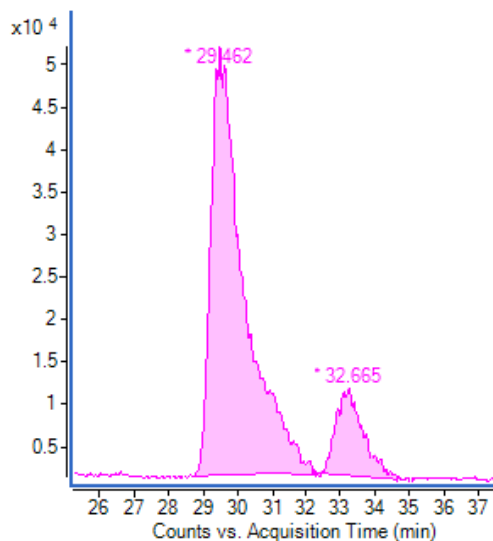
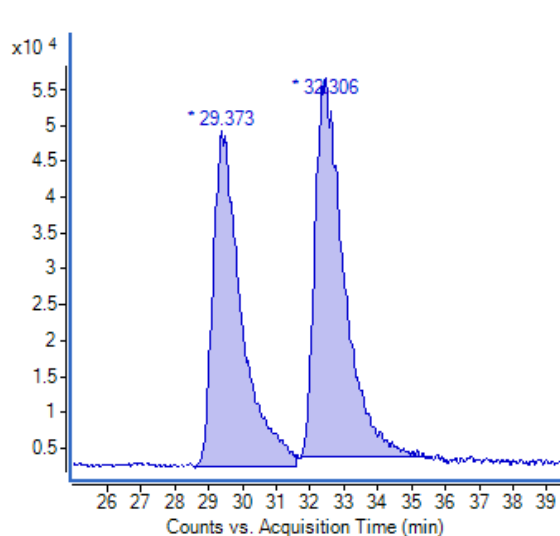
## 5.7 Synthesis of (E)-1-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-ylidene)methanamine (16)



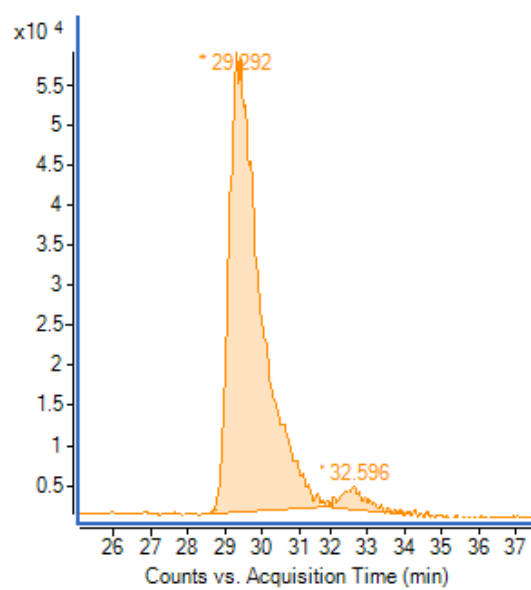
The enantiomeric excess were obtained by chiral HPLC analysis of the corresponding hydrolysed product (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-one) using an AD-H column (iPrOH-hexane, 0.2:99.8, 0.3mL/min, HPLC-MS); the major isomer  $t_r$  = 29.4min and the minor isomer  $t_r$  = 32.4min . Specific rotation:  $[\alpha]_D^{23} +56.2$  (c 0.53 in  $\text{CHCl}_3$  for a sample of 70ee%) and  $[\alpha]_D^{23} +52.5$  (c 0.53 in  $\text{CHCl}_3$  for a sample of 64ee%).

*Racemic*

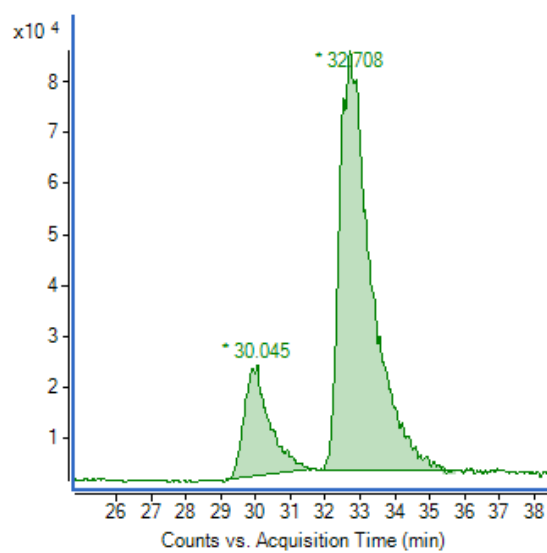
*71% ee*



92% ee



66% ee (*other enantiomer*)



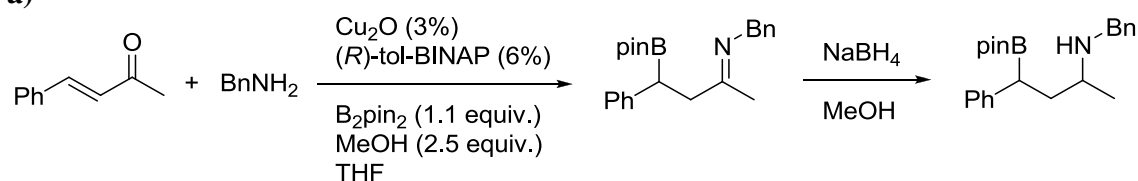
## 6. ReactIR

All *in situ* IR spectroscopy experiments (ReactIR) were carried out on the following instrument: ReactIR 15 with MCT detector; HappGenzel, DiComp (Diamond) probe connected *via* AgX 9.5 mm – 2 m fiber (Silver Halide); Sampling 2500 to 650  $\text{cm}^{-1}$ , 8 wave number resolution.

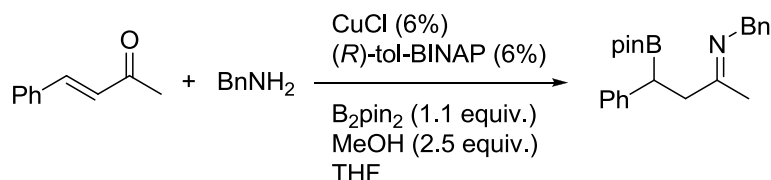
Reaction performed on a 1 mmol scale using the standard protocol as outlined in Section 2.

### Scheme 1.

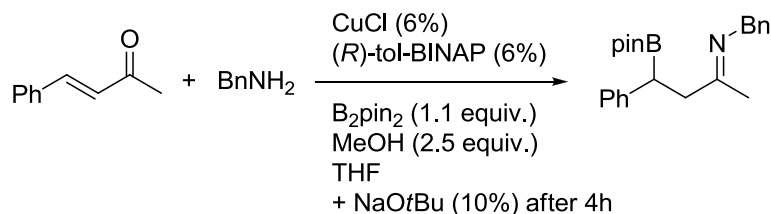
a)



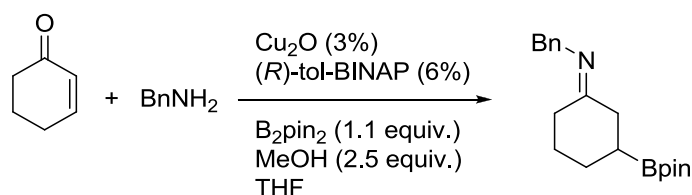
b)



c)

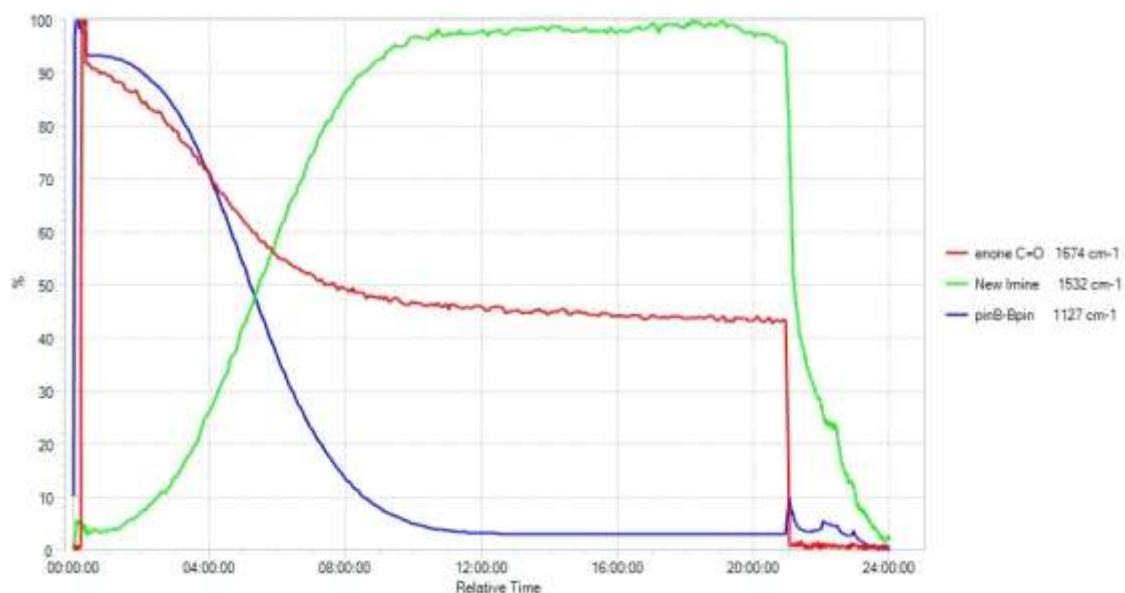


d)



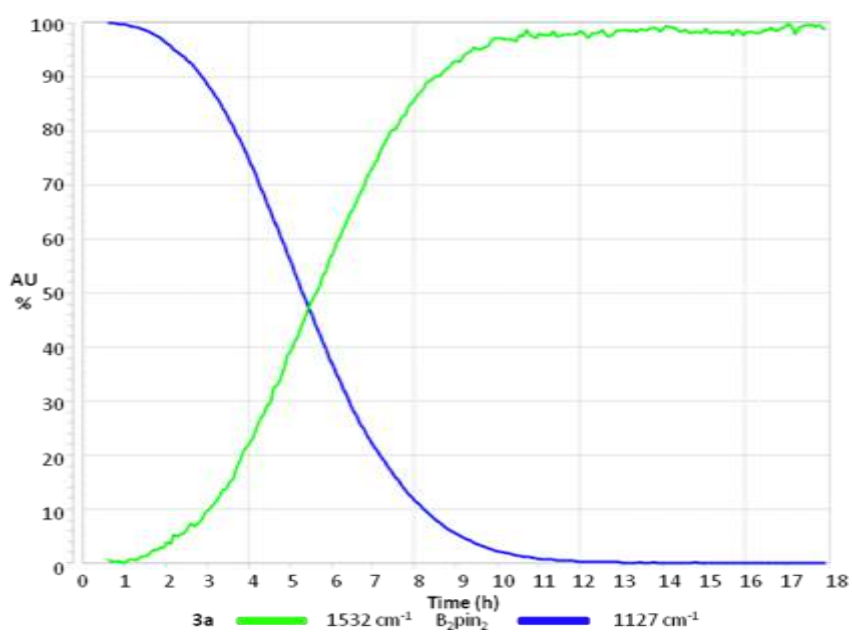
Peak overlap is placed between the  $\text{C}=\text{O}$  stretch of the starting enone and the  $\text{C}=\text{N}$  [a) and b)] of the product  $\beta$ -bprated imine. Therefore, alternative bands were trended for the imine product ( $1532\text{ cm}^{-1}$ ).

The images overpage have been unedited.

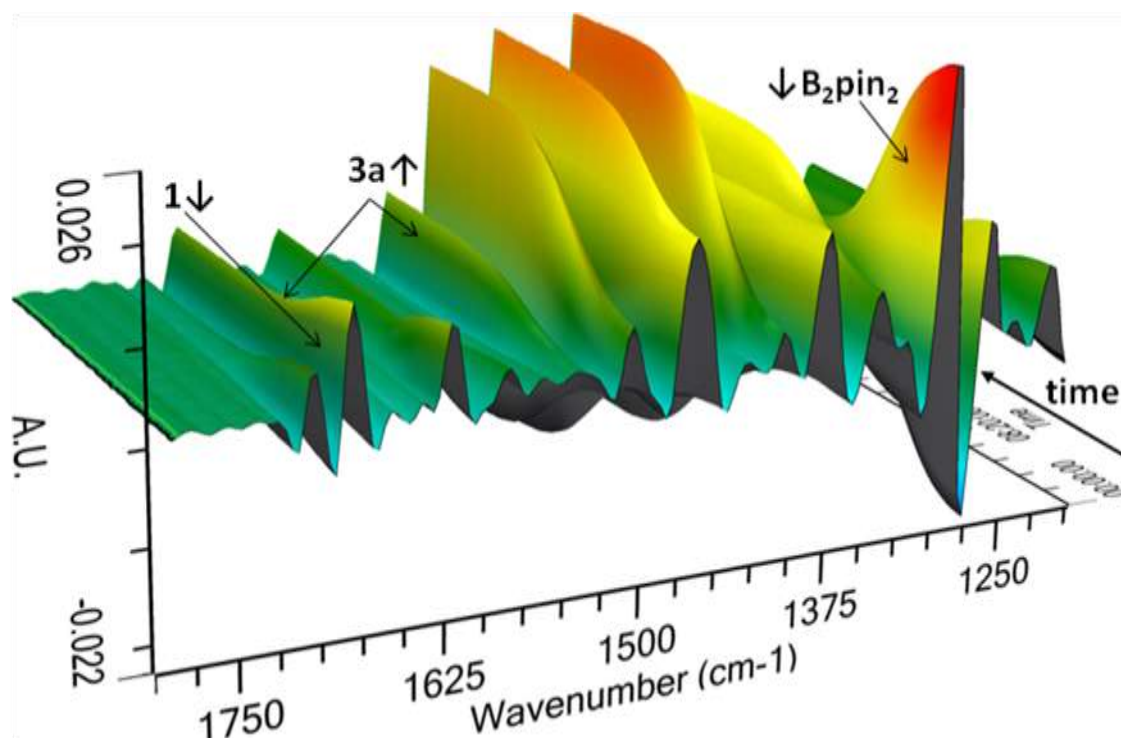


### ReactIR real time plot of Scheme 1a

Showing initial mixing (<1 h), reaction (1-12 h), reduction (>20 h)).

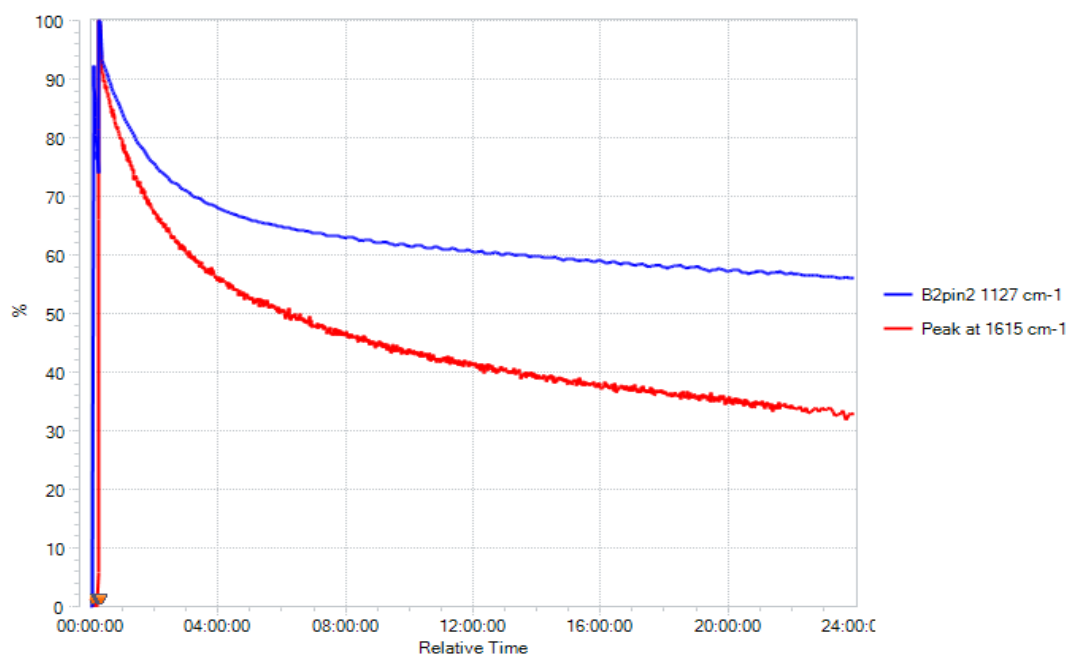


### ReactIR real time plot of Scheme 1a – as used in the main paper.



### ReactIR graphical output from Scheme 1a

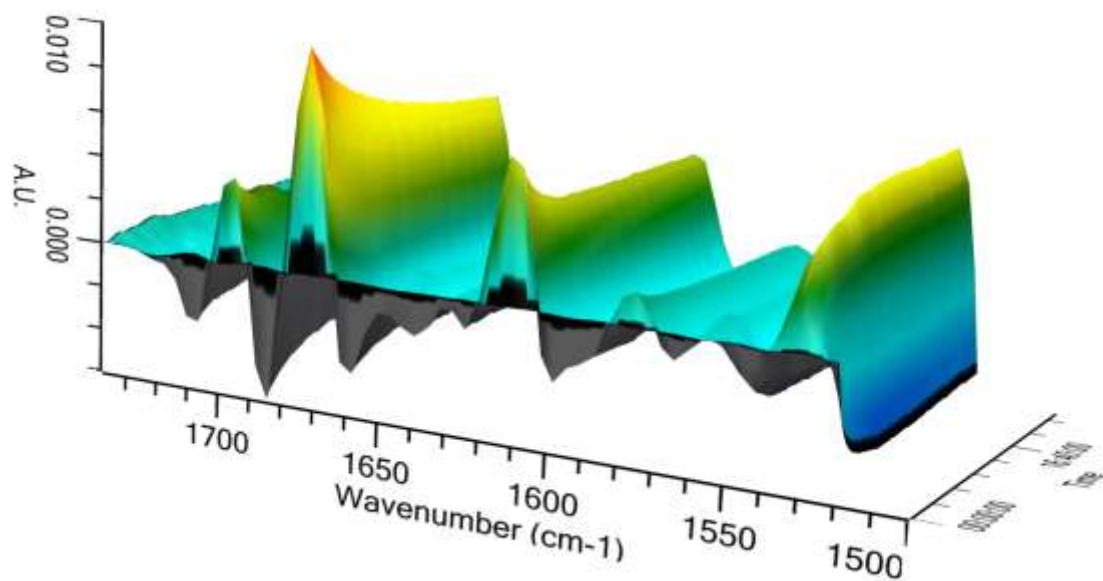
(Spectrum Math = 2<sup>nd</sup> Derivative, corrects for baseline fluctuations over time).



### ReactIR real time plot of Scheme 1b

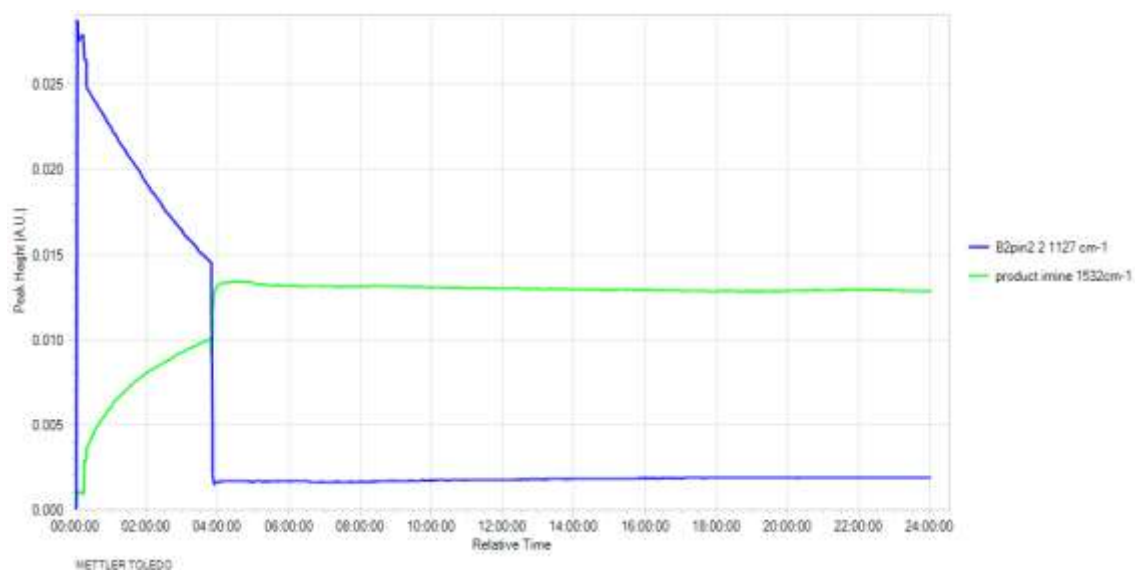
Showing initial mixing (<1 h), reaction (1-24+ h).





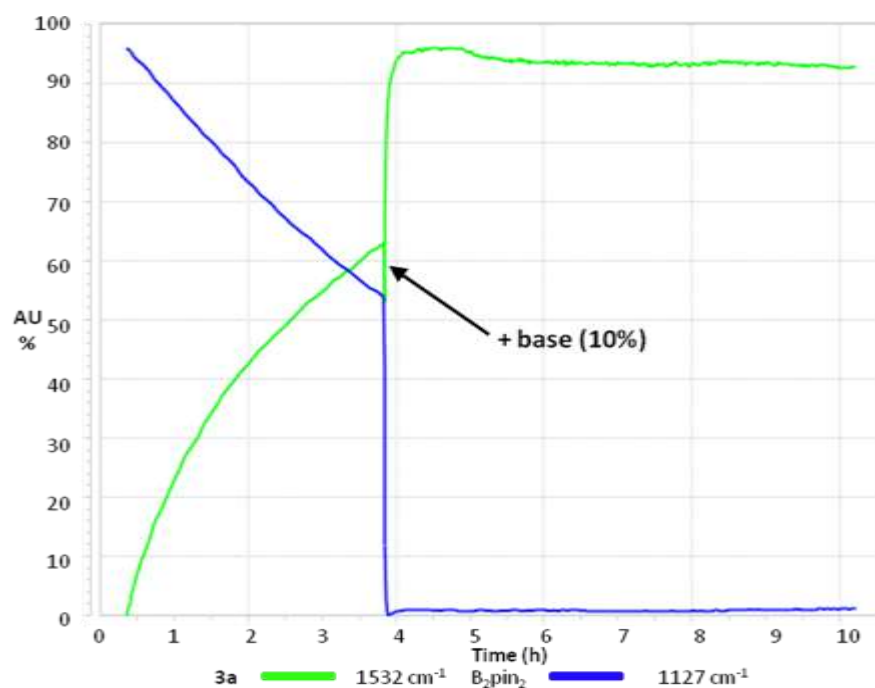
### ReactIR graphical output from Scheme 1b

(Spectrum Math = 2<sup>nd</sup> Derivative, corrects for baseline fluctuations over time).



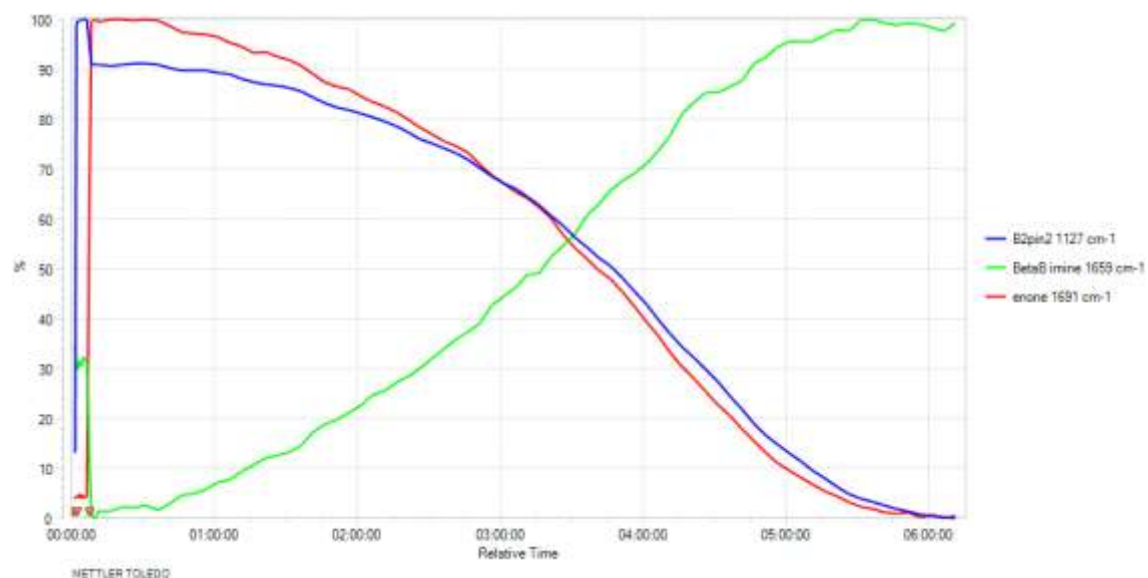
### ReactIR real time plot of Scheme 1c

(Spectrum Math = 2<sup>nd</sup> Derivative, corrects for baseline fluctuations over time).



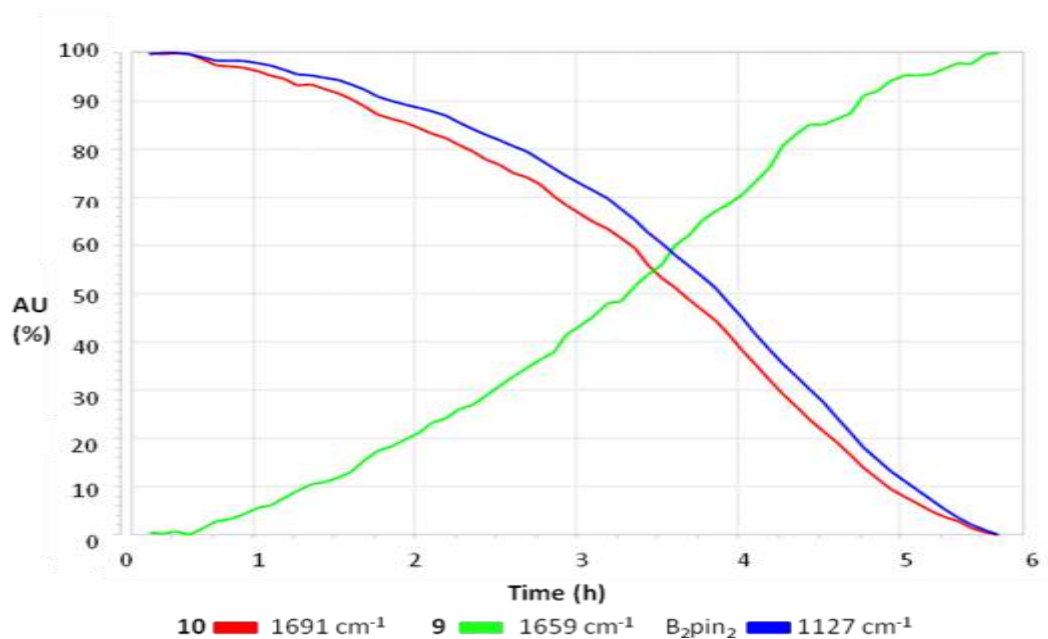
**ReactIR real time plot of Scheme 1c – as used in the main paper.**

(Spectrum Math = 2<sup>nd</sup> Derivative, corrects for baseline fluctuations over time).

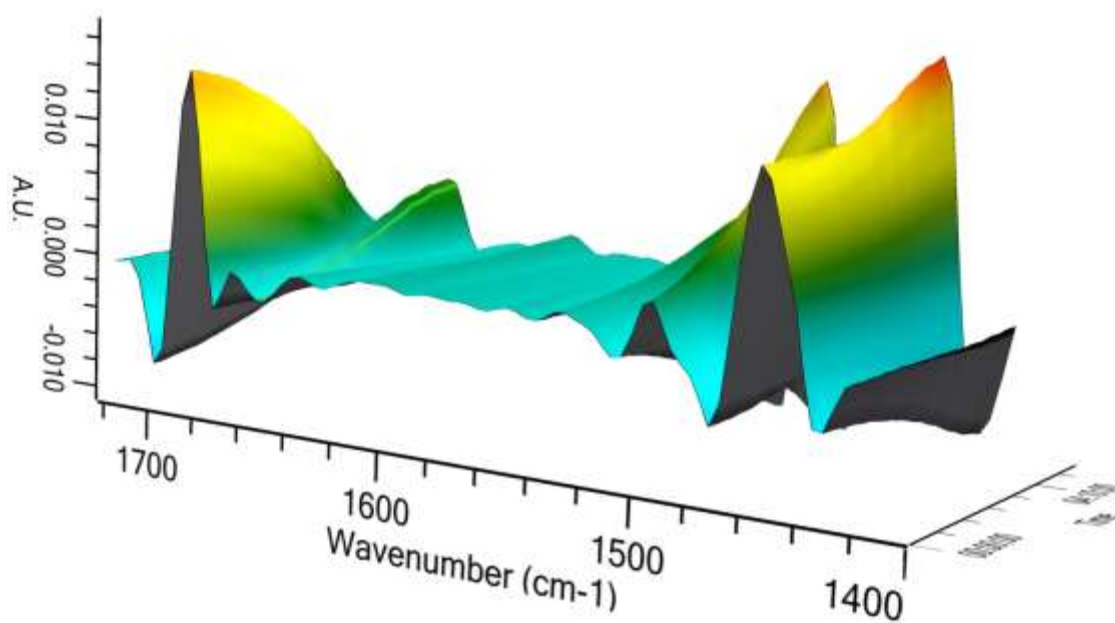


**ReactIR real time plot of Scheme 1d**

Showing initial mixing (<0.5 h), reaction (1-6 h).



ReactIR real time plot of Scheme 1d - as used in the main paper.



ReactIR graphical output from Scheme 1d

(Spectrum Math = 2<sup>nd</sup> Derivative, corrects for baseline fluctuations over time).

## 7. References

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1. For the experimental procedure of synthesis: Solé, C, Fernández, E. *Asian J. Chem*, **2009**, 4, 1790-1793.
  2. Solé, C; Whiting, A; Gulyás, H; Fernández, E. *Adv. Synth. Catal.*, **2011**, 353, 376-384.
  3. Solé, C.; Tatla, A.; Mata, J.A.; Whiting, A.; Gulyás, H.; Fernández, E. *Chem. Eur. J.* **2011**, 17, 14248-14257.
  4. Wu, H.; Radomkit, S.; O'Brien, J.M.; Hoveyda, A.H. *J. Am. Chem. Soc.*, **2012**, 134, 8277-8285.